

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 March 2003 (13.03.2003)

PCT

(10) International Publication Number
WO 03/020710 A1

(51) International Patent Classification⁷: **C07D 281/10**,
417/12, A61K 31/554, A61P 3/06

Molndal (SE). **BOSTROM, Stig, Jonas** [SE/SE]; S-431
83 Molndal (SE).

(21) International Application Number: PCT/GB02/03983

(74) Agents: **BRYANT, Tracey** et al.; Astrazeneca, Global In-
tellectual Property, Mereside, Alderley Park, Macclesfield,
Cheshire SK10 4TG (GB).

(22) International Filing Date: 30 August 2002 (30.08.2002)

(25) Filing Language: English

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VC, VN, YU, ZA, ZM, ZW.

(26) Publication Language: English

(30) Priority Data:
0121337.0 4 September 2001 (04.09.2001) GB

(71) Applicant (*for all designated States except MG, US*): **AS-
TRAZENECA AB** [SE/SE]; Sodertalje, S-151 85 (SE).

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for MG only*): **ASTRAZENECA UK LIM-
ITED** [GB/GB]; 15 Stanhope Gate, London, Greater Lon-
don W1Y 6LN (GB).

(72) Inventors; and

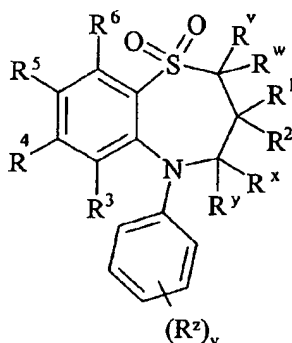
(75) Inventors/Applicants (*for US only*): **STARKE, Inge-
mar** [SE/SE]; S-431 83 Molndal (SE). **DAHLSTROM,**
Mikael, Ulf, Johan [FI/SE]; S-431 83 Molndal (SE).
BLOMBERG, David [SE/SE]; S-431 83 Molndal (SE).
ALENFALK, Suzanne [SE/SE]; S-431 83 Molndal (SE).
NORDBERG, Peter [SE/SE]; S-431 83 Molndal (SE).
WALLBERG, Andreas, Christer [SE/SE]; S-431 83

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: **BENZOTHAZEPINE DERIVATIVES**



(I)

(57) Abstract: The present invention relates to compounds of formula (I), wherein variable groups are as defined within; pharmaceutically acceptable salts, solvates, solvates of such salts and prodrugs thereof and their use as ileal bile acid transport (IBAT) inhibitors for the treatment of hyperlipidaemia. Processes for their manufacture and pharmaceutical compositions containing them are also described.

BENZOTHIAZEPINE DERIVATIVES

This invention relates to benzothiazepine derivatives, or pharmaceutically acceptable salts, solvates, solvates of such salts and prodrugs thereof. These benzothiazepines possess
5 ileal bile acid transport (IBAT) inhibitory activity and accordingly have value in the treatment of disease states associated with hyperlipidaemic conditions and they are useful in methods of treatment of a warm-blooded animal, such as man. The invention also relates to processes for the manufacture of said benzothiazepine derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments to inhibit IBAT in a
10 warm-blooded animal, such as man.

It is well-known that hyperlipidaemic conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein cholesterol are major risk factors for cardiovascular atherosclerotic disease (for instance "Coronary Heart Disease: Reducing the Risk; a Worldwide View" Assman G., Carmena R. Cullen P. *et al*; Circulation
15 1999, 100, 1930-1938 and "Diabetes and Cardiovascular Disease: A Statement for Healthcare Professionals from the American Heart Association" Grundy S, Benjamin I., Burke G., *et al*; Circulation, 1999, 100, 1134-46). Interfering with the circulation of bile acids within the lumen of the intestinal tracts is found to reduce the level of cholesterol. Previous established therapies to reduce the concentration of cholesterol involve, for instance, treatment with
20 HMG-CoA reductase inhibitors, preferably statins such as simvastatin and fluvastatin, or treatment with bile acid binders, such as resins. Frequently used bile acid binders are for instance cholestyramine and cholestipol. One recently proposed therapy ("Bile Acids and Lipoprotein Metabolism: a Renaissance for Bile Acids in the Post Statin Era" Angelin B, Eriksson M, Rudling M; Current Opinion on Lipidology, 1999, 10, 269-74) involved the
25 treatment with substances with an IBAT inhibitory effect.

Re-absorption of bile acid from the gastro-intestinal tract is a normal physiological process which mainly takes place in the ileum by the IBAT mechanism. Inhibitors of IBAT can be used in the treatment of hypercholesterolaemia (see for instance "Interaction of bile acids and cholesterol with nonsystemic agents having hypocholesterolaemic properties",
30 Biochemica et Biophysica Acta, 1210 (1994) 255- 287). Thus, suitable compounds having such inhibitory IBAT activity are also useful in the treatment of hyperlipidaemic conditions.

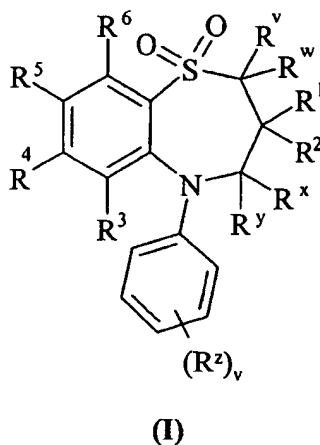
Compounds possessing such IBAT inhibitory activity have been described, see for instance the compounds described in WO 93/16055, WO 94/18183, WO 94/18184, WO

96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/38182, WO 99/35135, WO 98/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, WO 01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/68906, WO 01/66533, WO 02/50051 and EP 0 864 582.

5 A further aspect of this invention relates to the use of the compounds of the invention in the treatment of dyslipidemic conditions and disorders such as hyperlipidaemia, hypertriglyceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia, hyperlipoproteinemia and hypoalphalipoproteinemia (low HDL). In addition, these
10 compounds are expected to be useful for the prevention and treatment of different clinical conditions such as atherosclerosis, arteriosclerosis, arrhythmia, hyper-thrombotic conditions, vascular dysfunction, endothelial dysfunction, heart failure, coronary heart diseases, cardiovascular diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, inflammation of cardiovascular tissues such as heart, valves, vasculature, arteries and veins,
15 aneurisms, stenosis, restenosis, vascular plaques, vascular fatty streaks, leukocytes, monocytes and/or macrophage infiltration, intimal thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks.

The present invention is based on the discovery that certain benzothiazepine compounds surprisingly inhibit IBAT. Such properties are expected to be of value in the
20 treatment of disease states associated with hyperlipidaemic conditions.

Accordingly, the present invention provides a compound of formula (I):



wherein:

25 R^v and R^w are independently selected from hydrogen or C_{1-6} alkyl;

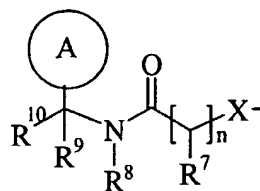
One of R^1 and R^2 are selected from hydrogen or C_{1-6} alkyl and the other is selected from C_{1-6} alkyl;

R^x and R^y are independently selected from hydrogen or C_{1-6} alkyl, or one of R^x and R^y is hydrogen or C_{1-6} alkyl and the other is hydroxy or C_{1-6} alkoxy;

5 R^z is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl)₂amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkylS(O)_a wherein a is 0 to 2, C_{1-6} alkoxycarbonyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl)₂sulphamoyl;

10 v is 0-5;

one of R^4 and R^5 is a group of formula (IA):



(IA)

R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen, halo, 15 nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl)₂amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkylS(O)_a wherein a is 0 to 2, C_{1-6} alkoxycarbonyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl)₂sulphamoyl; wherein R^3 and R^6 and the other of 20 R^4 and R^5 may be optionally substituted on carbon by one or more R^{17} ;

X is -O-, -N(R^a)-, -S(O)_b- or -CH(R^a)-; wherein R^a is hydrogen or C_{1-6} alkyl and b is 0-2;

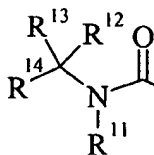
Ring A is aryl or heteroaryl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R^{18} ;

25 R^7 is hydrogen, C_{1-6} alkyl, carbocyclyl or heterocyclyl; wherein R^7 is optionally substituted on carbon by one or more substituents selected from R^{19} ; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{20} ;

R^8 is hydrogen or C_{1-6} alkyl;

R^9 is hydrogen or C_{1-6} alkyl;

- R^{10} is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy, C_{1-10} alkanoyl, C_{1-10} alkanoyloxy, N -(C_{1-10} alkyl)amino, N,N -(C_{1-10} alkyl)₂amino, N,N,N -(C_{1-10} alkyl)₃ammonio, C_{1-10} alkanoylamino, N -(C_{1-10} alkyl)carbamoyl, N,N -(C_{1-10} alkyl)₂carbamoyl, C_{1-10} alkylS(O)_a wherein a is 0 to 2, N -(C_{1-10} alkyl)sulphamoyl, N,N -(C_{1-10} alkyl)₂sulphamoyl, N -(C_{1-10} alkyl)sulphamoylamino, N,N -(C_{1-10} alkyl)₂sulphamoylamino, C_{1-10} alkoxycarbonylamino, carbocyclyl, carbocyclyl C_{1-10} alkyl, heterocyclyl, heterocyclyl C_{1-10} alkyl, carbocyclyl-(C_{1-10} alkylene)_p- R^{21} -(C_{1-10} alkylene)_q- or heterocyclyl-(C_{1-10} alkylene)_r- R^{22} -(C_{1-10} alkylene)_s; wherein R^{10} is optionally substituted on carbon by one or more substituents selected from R^{23} ; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{24} ; or R^{10} is a group of formula (IB):



(IB)

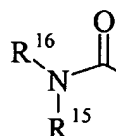
wherein:

R^{11} is hydrogen or C_{1-6} alkyl;

- R^{12} and R^{13} are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy, C_{1-10} alkanoyl, C_{1-10} alkanoyloxy, N -(C_{1-10} alkyl)amino, N,N -(C_{1-10} alkyl)₂amino, C_{1-10} alkanoylamino, N -(C_{1-10} alkyl)carbamoyl, N,N -(C_{1-10} alkyl)₂carbamoyl, C_{1-10} alkylS(O)_a wherein a is 0 to 2, N -(C_{1-10} alkyl)sulphamoyl, N,N -(C_{1-10} alkyl)₂sulphamoyl, N -(C_{1-10} alkyl)sulphamoylamino, N,N -(C_{1-10} alkyl)₂sulphamoylamino, carbocyclyl or heterocyclyl; wherein R^{12} and R^{13} may be independently optionally substituted on carbon by one or more substituents selected from R^{25} ; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{26} ;

- R^{14} is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy, C_{1-10} alkanoyl, C_{1-10} alkanoyloxy, N -(C_{1-10} alkyl)amino, N,N -(C_{1-10} alkyl)₂amino,

- N,N,N*-(C₁₋₁₀alkyl)₃ammonio, C₁₋₁₀alkanoylamino, *N*-(C₁₋₁₀alkyl)carbamoyl,
N,N-(C₁₋₁₀alkyl)₂carbamoyl, C₁₋₁₀alkylS(O)_a wherein a is 0 to 2, *N*-(C₁₋₁₀alkyl)sulphamoyl,
N,N-(C₁₋₁₀alkyl)₂sulphamoyl, *N*-(C₁₋₁₀alkyl)sulphamoylamino,
N,N-(C₁₋₁₀alkyl)₂sulphamoylamino, C₁₋₁₀alkoxycarbonylamino, carbocyclyl,
 5 carbocyclylC₁₋₁₀alkyl, heterocyclyl, heterocyclylC₁₋₁₀alkyl,
 carbocyclyl-(C₁₋₁₀alkylene)_p-R²⁷-(C₁₋₁₀alkylene)_q- or
 heterocyclyl-(C₁₋₁₀alkylene)_r-R²⁸-(C₁₋₁₀alkylene)_s-; wherein R¹⁴ may be optionally substituted
 on carbon by one or more substituents selected from R²⁹; and wherein if said heterocyclyl
 contains an -NH- group, that nitrogen may be optionally substituted by a group selected from
 10 R³⁰; or R¹⁴ is a group of formula (IC):



(IC)

- R¹⁵ is hydrogen or C₁₋₆alkyl;
 R¹⁶ is hydrogen or C₁₋₆alkyl; wherein R¹⁶ may be optionally substituted on carbon by
 15 one or more groups selected from R³¹;
 n is 1-3; wherein the values of R⁷ may be the same or different;
 R¹⁷, R¹⁸, R¹⁹, R²³, R²⁵, R²⁹ or R³¹ are independently selected from halo, nitro, cyano,
 hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, amidino,
 C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxy, C₁₋₁₀alkanoyl, C₁₋₁₀alkanoyloxy,
 20 (C₁₋₁₀alkyl)₃silyl, *N*-(C₁₋₁₀alkyl)amino, *N,N*-(C₁₋₁₀alkyl)₂amino, *N,N,N*-(C₁₋₁₀alkyl)₃ammonio,
 C₁₋₁₀alkanoylamino, *N*-(C₁₋₁₀alkyl)carbamoyl, *N,N*-(C₁₋₁₀alkyl)₂carbamoyl, C₁₋₁₀alkylS(O)_a
 wherein a is 0 to 2, *N*-(C₁₋₁₀alkyl)sulphamoyl, *N,N*-(C₁₋₁₀alkyl)₂sulphamoyl,
N-(C₁₋₁₀alkyl)sulphamoylamino, *N,N*-(C₁₋₁₀alkyl)₂sulphamoylamino,
 C₁₋₁₀alkoxycarbonylamino, carbocyclyl, carbocyclylC₁₋₁₀alkyl, heterocyclyl,
 25 heterocyclylC₁₋₁₀alkyl, carbocyclyl-(C₁₋₁₀alkylene)_p-R³²-(C₁₋₁₀alkylene)_q- or
 heterocyclyl-(C₁₋₁₀alkylene)_r-R³³-(C₁₋₁₀alkylene)_s-; wherein R¹⁷, R¹⁸, R¹⁹, R²³, R²⁵, R²⁹ or R³¹
 may be independently optionally substituted on carbon by one or more R³⁴; and wherein if
 said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a
 group selected from R³⁵;

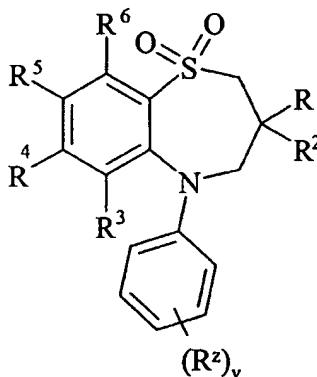
R^{21} , R^{22} , R^{27} , R^{28} , R^{32} or R^{33} are independently selected from -O-, $-NR^{36}-$, $-S(O)_x-$, $-NR^{36}C(O)NR^{36}-$, $-NR^{36}C(S)NR^{36}-$, $-OC(O)N=C-$, $-NR^{36}C(O)-$ or $-C(O)NR^{36}-$; wherein R^{36} is selected from hydrogen or C_{1-6} alkyl, and x is 0-2;

p, q, r and s are independently selected from 0-2;

- 5 R^{34} is selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, formyl, acetyl, formamido, acetylamino, acetoxy, methylamino, dimethylamino, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, *N*-methylsulphamoyl, *N,N*-dimethylsulphamoyl, *N*-methylsulphamoylamino and
- 10 *N,N*-dimethylsulphamoylamino;

R^{20} , R^{24} , R^{26} , R^{30} or R^{35} are independently selected from C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxycarbonyl, carbamoyl, *N*-(C_{1-6} alkyl)carbamoyl, *N,N*-(C_{1-6} alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

- 15 Accordingly, in another aspect of the present invention there is provided a compound of formula (I):



(I)

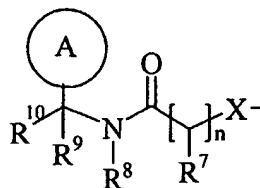
wherein:

- 20 One of R^1 and R^2 are selected from hydrogen or C_{1-6} alkyl and the other is selected from C_{1-6} alkyl;

- R^2 is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, *N*-(C_{1-6} alkyl)amino, *N,N*-(C_{1-6} alkyl)₂amino, C_{1-6} alkanoylamino, *N*-(C_{1-6} alkyl)carbamoyl,
- 25 *N,N*-(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkylS(O)_a wherein a is 0 to 2, C_{1-6} alkoxycarbonyl, *N*-(C_{1-6} alkyl)sulphamoyl and *N,N*-(C_{1-6} alkyl)₂sulphamoyl;

v is 0-5;

one of R^4 and R^5 is a group of formula (IA):



(IA)

- 5 R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkylS(O) $_a$ wherein a is 0 to 2, C_{1-6} alkoxycarbonyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl) $_2$ sulphamoyl; wherein R^3 and R^6 and the other of R^4 and R^5 may be optionally substituted on carbon by one or more R^{17} ;

X is -O-, -N(R^a)-, -S(O) $_b$ - or -CH(R^a)-; wherein R^a is hydrogen or C_{1-6} alkyl and b is 0-2;

- 15 **Ring A** is aryl or heteroaryl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R^{18} ;

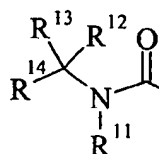
R^7 is hydrogen, C_{1-6} alkyl, carbocyclyl or heterocyclyl; wherein R^7 is optionally substituted on carbon by one or more substituents selected from R^{19} ; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{20} ;

- 20 R^8 is hydrogen or C_{1-6} alkyl;

R^9 is hydrogen or C_{1-6} alkyl;

- R^{10} is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy, C_{1-10} alkanoyl, C_{1-10} alkanoyloxy, N -(C_{1-10} alkyl)amino, N,N -(C_{1-10} alkyl) $_2$ amino, N,N,N -(C_{1-10} alkyl) $_3$ ammonio, C_{1-10} alkanoylamino, N -(C_{1-10} alkyl)carbamoyl, N,N -(C_{1-10} alkyl) $_2$ carbamoyl, C_{1-10} alkylS(O) $_a$ wherein a is 0 to 2, N -(C_{1-10} alkyl)sulphamoyl, N,N -(C_{1-10} alkyl) $_2$ sulphamoyl, N -(C_{1-10} alkyl)sulphamoylamino, N,N -(C_{1-10} alkyl) $_2$ sulphamoylamino, C_{1-10} alkoxycarbonylamino, carbocyclyl, carbocyclyl C_{1-10} alkyl, heterocyclyl, heterocyclyl C_{1-10} alkyl,

- carbocyclyl-(C₁₋₁₀alkylene)_p-R²¹-(C₁₋₁₀alkylene)_q- or
 heterocyclyl-(C₁₋₁₀alkylene)_r-R²²-(C₁₋₁₀alkylene)_s-; wherein R¹⁰ is optionally substituted on
 carbon by one or more substituents selected from R²³; and wherein if said heterocyclyl
 contains an -NH- group, that nitrogen may be optionally substituted by a group selected from
 5 R²⁴; or R¹⁰ is a group of formula (IB):

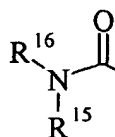


(IB)

wherein:

- R¹¹ is hydrogen or C₁₋₆alkyl;
- 10 R¹² and R¹³ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₁₋₁₀alkoxy, C₁₋₁₀alkanoyl, C₁₋₁₀alkanoyloxy, *N*-(C₁₋₁₀alkyl)amino, *N,N*-(C₁₋₁₀alkyl)₂amino, C₁₋₁₀alkanoylamino, *N*-(C₁₋₁₀alkyl)carbamoyl, *N,N*-(C₁₋₁₀alkyl)₂carbamoyl, C₁₋₁₀alkylS(O)_a wherein a is 0 to 2, *N*-(C₁₋₁₀alkyl)sulphamoyl, *N,N*-(C₁₋₁₀alkyl)₂sulphamoyl,
- 15 *N*-(C₁₋₁₀alkyl)sulphamoylamino, *N,N*-(C₁₋₁₀alkyl)₂sulphamoylamino, carbocyclyl or heterocyclyl; wherein R¹² and R¹³ may be independently optionally substituted on carbon by one or more substituents selected from R²⁵; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R²⁶;
- R¹⁴ is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl,
- 20 C₁₋₁₀alkoxy, C₁₋₁₀alkanoyl, C₁₋₁₀alkanoyloxy, *N*-(C₁₋₁₀alkyl)amino, *N,N*-(C₁₋₁₀alkyl)₂amino, *N,N,N*-(C₁₋₁₀alkyl)₃ammonio, C₁₋₁₀alkanoylamino, *N*-(C₁₋₁₀alkyl)carbamoyl, *N,N*-(C₁₋₁₀alkyl)₂carbamoyl, C₁₋₁₀alkylS(O)_a wherein a is 0 to 2, *N*-(C₁₋₁₀alkyl)sulphamoyl, *N,N*-(C₁₋₁₀alkyl)₂sulphamoyl, *N*-(C₁₋₁₀alkyl)sulphamoylamino,
- 25 *N,N*-(C₁₋₁₀alkyl)₂sulphamoylamino, C₁₋₁₀alkoxycarbonylamino, carbocyclyl, carbocyclylC₁₋₁₀alkyl, heterocyclyl, heterocyclylC₁₋₁₀alkyl, carbocyclyl-(C₁₋₁₀alkylene)_p-R²⁷-(C₁₋₁₀alkylene)_q- or heterocyclyl-(C₁₋₁₀alkylene)_r-R²⁸-(C₁₋₁₀alkylene)_s-; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²⁹; and wherein if said heterocyclyl

contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{30} ; or R^{14} is a group of formula (IC):



(IC)

- 5 R^{15} is hydrogen or C_{1-6} alkyl;
 R^{16} is hydrogen or C_{1-6} alkyl; wherein R^{16} may be optionally substituted on carbon by one or more groups selected from R^{31} ;
 n is 1-3; wherein the values of R^7 may be the same or different;
 $R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29}$ or R^{31} are independently selected from halo, nitro, cyano,
10 hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy, C_{1-10} alkanoyl, C_{1-10} alkanoyloxy, N -(C_{1-10} alkyl)amino, N,N -(C_{1-10} alkyl)₂amino, N,N,N -(C_{1-10} alkyl)₃ammonio, C_{1-10} alkanoylamino, N -(C_{1-10} alkyl)carbamoyl, N,N -(C_{1-10} alkyl)₂carbamoyl, C_{1-10} alkylS(O)_a wherein a is 0 to 2, N -(C_{1-10} alkyl)sulphamoyl, N,N -(C_{1-10} alkyl)₂sulphamoyl, N -(C_{1-10} alkyl)sulphamoylamino,
15 N,N -(C_{1-10} alkyl)₂sulphamoylamino, C_{1-10} alkoxycarbonylamino, carbocyclyl, carbocyclyl C_{1-10} alkyl, heterocyclyl, heterocyclyl C_{1-10} alkyl, carbocyclyl-(C_{1-10} alkylene)_p- R^{32} -(C_{1-10} alkylene)_q- or heterocyclyl-(C_{1-10} alkylene)_r- R^{33} -(C_{1-10} alkylene)_s-; wherein $R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29}$ or R^{31} may be independently optionally substituted on carbon by one or more R^{34} ; and wherein if
20 said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{35} ;
 $R^{21}, R^{22}, R^{27}, R^{28}, R^{32}$ or R^{33} are independently selected from -O-, -NR³⁶-, -S(O)_x-, -NR³⁶C(O)NR³⁶-, -NR³⁶C(S)NR³⁶-, -OC(O)N=C-, -NR³⁶C(O)- or -C(O)NR³⁶-; wherein R^{36} is selected from hydrogen or C_{1-6} alkyl, and x is 0-2;
25 p, q, r and s are independently selected from 0-2;
 R^{34} is selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, formyl, acetyl, formamido, acetylamino, acetoxymethyl, methylamino, dimethylamino, N -methylcarbamoyl, N,N -dimethylcarbamoyl, methylthio, methylsulphinyl,

mesyl, *N*-methylsulphamoyl, *N,N*-dimethylsulphamoyl, *N*-methylsulphamoylamino and *N,N*-dimethylsulphamoylamino;

R^{20} , R^{24} , R^{26} , R^{30} or R^{35} are independently selected from C_{1-6} alkyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl, C_{1-6} alkoxycarbonyl, carbamoyl, *N*-(C_{1-6} alkyl)carbamoyl,
5 *N,N*-(C_{1-6} alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;
or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, " C_{1-6} alkyl" includes C_{1-4} alkyl, C_{1-3} alkyl, propyl, isopropyl
10 and *t*-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. A similar convention applies to other radicals, for example " $phenylC_{1-6}alkyl$ " would include $phenylC_{1-6}alkyl$, benzyl, 1-phenylethyl and 2-phenylethyl. The term "halo" refers to fluoro, chloro, bromo and
15 iodo.

Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

"Heteroaryl" is a totally unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom, particularly 1-3 atoms, are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Preferably "heteroaryl" refers to a totally unsaturated, monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Examples and
20 suitable values of the term "heteroaryl" are thienyl, isoxazolyl, imidazolyl, pyrrolyl, thiadiazolyl, isothiazolyl, triazolyl, pyranlyl, indolyl, pyrimidyl, pyrazinyl, pyridazinyl, pyridyl and quinolyl. Preferably the term "heteroaryl" refers to thienyl or indolyl. "Heteroaryl" is not tetrazolyl.

"Aryl" is a totally unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms. Preferably "aryl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9
30 or 10 atoms. Suitable values for "aryl" include phenyl or naphthyl. Particularly "aryl" is phenyl.

A "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom, particularly 1-3 atoms, are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH₂- group can optionally be replaced by a -C(O)- or a ring sulphur atom
 5 may be optionally oxidised to form the S-oxides. Preferably a "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH₂- group can optionally be replaced by a -C(O)- or a ring sulphur atom may be optionally oxidised to form S-oxide(s). Examples and
 10 suitable values of the term "heterocyclyl" are thiazolidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidinonyl, 2,5-dioxopyrrolidinyl, 2-benzoxazolinonyl, 1,1-dioxotetrahydrothienyl, 2,4-dioxoimidazolidinyl, 2-oxo-1,3,4-(4-triazolinyl), 2-oxazolidinonyl, 5,6-dihydrouacetyl, 1,3-benzodioxolyl, 1,2,4-oxadiazolyl, 2-azabicyclo[2.2.1]heptyl, 4-thiazolidonyl, morpholino, 2-oxotetrahydrofuranlyl, tetrahydrofuranlyl, 2,3-dihydrobenzofuranlyl, benzothienyl,
 15 tetrahydropyranlyl, piperidyl, 1-oxo-1,3-dihydroisoindolyl, piperazinyl, thiomorpholino, 1,1-dioxothiomorpholino, tetrahydropyranlyl, 1,3-dioxolanyl, homopiperazinyl, thienyl, isoxazolyl, imidazolyl, pyrrolyl, thiadiazolyl, isothiazolyl, 1,2,4-triazolyl, 1,3,4-triazolyl, pyranlyl, indolyl, pyrimidyl, thiazolyl, pyrazinyl, pyridazinyl, pyridyl, 4-pyridonyl, quinolyl and 1-isoquinolonyl. "Heterocyclyl" is not tetrazolyl.

20 A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms; wherein a -CH₂- group can optionally be replaced by a -C(O)-. Preferably "carbocyclyl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "carbocyclyl" include cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl,
 25 naphthyl, tetralinyl, indanyl or 1-oxoindanyl. Particularly "carbocyclyl" is cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl or 1-oxoindanyl.

An example of "C₁₋₁₀alkanoyloxy" and "C₁₋₆alkanoyloxy" is acetoxy. Examples of "C₁₋₁₀alkoxycarbonyl" and "C₁₋₆alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl,
 30 *n*- and *t*-butoxycarbonyl. Examples of "C₁₋₁₀alkoxy" and "C₁₋₆alkoxy" include methoxy, ethoxy and propoxy. Examples of "C₁₋₁₀alkanoylamino" and "C₁₋₆alkanoylamino" include formamido, acetamido and propionylamino. Examples of "C₁₋₁₀alkylS(O)_a wherein a is 0 to 2" and "C₁₋₆alkylS(O)_a wherein a is 0 to 2" include methylthio, ethylthio, methylsulphinyl,

ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C₁₋₁₀alkanoyl" and "C₁₋₆alkanoyl" include C₁₋₃alkanoyl, propionyl and acetyl. Examples of "*N*-C₁₋₁₀alkylamino" and "*N*-C₁₋₆alkylamino" include methylamino and ethylamino. Examples of "*N,N*-(C₁₋₁₀alkyl)₂amino" and "*N,N*-(C₁₋₆alkyl)₂amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C₂₋₁₀alkenyl" and "C₂₋₆alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C₂₋₁₀alkynyl" and "C₂₋₆alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C₁₋₁₀alkyl)sulphamoyl" and "*N*-(C₁₋₆alkyl)sulphamoyl" are *N*-(C₁₋₃alkyl)sulphamoyl, *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N*-(C₁₋₁₀alkyl)₂sulphamoyl" and "*N*-(C₁₋₆alkyl)₂sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N*-(C₁₋₁₀alkyl)carbamoyl" and "*N*-(C₁₋₆alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C₁₋₁₀alkyl)₂carbamoyl" and "*N,N*-(C₁₋₆alkyl)₂carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl. Example of "C₁₋₁₀alkylsulphonyl" and "C₁₋₆alkylsulphonyl" are mesyl and ethylsulphonyl. Examples of "*N,N,N*-(C₁₋₁₀alkyl)₃ammonio" and "*N,N,N*-(C₁₋₆alkyl)₃ammonio" are trimethylamino and methyldiethylamino. Examples of "C₁₋₁₀alkoxycarbonylamino" and "C₁₋₆alkoxycarbonylamino" are methoxycarbonylamino and *t*-butoxycarbonylamino. Examples of "*N*-(C₁₋₁₀alkyl)sulphamoylamino" and "*N*-(C₁₋₆alkyl)sulphamoylamino" are *N*-methylsulphamoylamino and *N*-ethylsulphamoylamino. Examples of "*N,N*-(C₁₋₁₀alkyl)₂sulphamoylamino" and "*N,N*-(C₁₋₆alkyl)₂sulphamoylamino" are *N,N*-dimethylsulphamoylamino and *N*-methyl-*N*-ethylsulphamoylamino. Examples of "C₁₋₁₀alkylthio" and "C₁₋₆alkylthio" are methylthio and ethylthio. Examples of "carbocyclylC₁₋₁₀alkyl" include benzyl and phenethyl. Examples of "heterocyclylC₁₋₁₀alkyl" include morpholinopropyl and pyridylmethyl. Examples of "(C₁₋₁₀alkyl)₃silyl" are trimethylsilyl and triethylsilyl.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric, acetate or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt

with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The compounds of the formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula (I).

5 examples of pro-drugs include *in vivo* hydrolysable esters and *in vivo* hydrolysable amides of a compound of the formula (I).

An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically
10 acceptable esters for carboxy include C₁₋₆alkoxymethyl esters for example methoxymethyl, C₁₋₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C₃₋₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁₋₆alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be
15 formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α -acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and
20 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked
25 from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

A suitable value for an *in vivo* hydrolysable amide of a compound of the formula (I) containing a carboxy group is, for example, a *N*-C₁₋₆alkyl or *N,N*-di-C₁₋₆alkyl amide such as *N*-methyl, *N*-ethyl, *N*-propyl, *N,N*-dimethyl, *N*-ethyl-*N*-methyl or *N,N*-diethyl amide.

Some compounds of the formula (I) may have chiral centres and/or geometric isomeric
30 centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess IBAT inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess IBAT inhibitory activity.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess IBAT inhibitory activity.

Particular values are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

R^v and R^w are both hydrogen.

10 R^1 and R^2 are independently selected from C_{1-4} alkyl.

One of R^1 and R^2 is ethyl or propyl and the other is butyl.

One of R^1 and R^2 is ethyl and the other is butyl.

R^1 and R^2 are both butyl.

One of R^1 and R^2 is ethyl and the other is butyl, or R^1 and R^2 are both butyl.

15 R^x and R^y are independently selected from hydrogen or C_{1-6} alkyl.

R^x and R^y are both hydrogen.

R^z is C_{1-4} alkyl.

v is 0-2.

v is 0.

20 R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen and C_{1-6} alkylthio.

R^3 and R^6 are hydrogen.

R^4 is halo.

R^4 is bromo or chloro.

25 R^4 is C_{1-6} alkoxy.

R^4 is ethoxy or methoxy.

R^4 is methoxy.

R^4 is ethylthio or methylthio.

R^4 is methylthio.

30 R^4 is hydrogen.

R^4 is hydrogen or methylthio.

R^5 is methylthio.

R^4 is a group of formula (IA) as depicted above.

R⁵ is a group of formula (IA) as depicted above.

R⁴ is methylthio and R⁵ is a group of formula (IA) as depicted above.

R⁵ is methylthio and R⁴ is a group of formula (IA) as depicted above.

R⁵ is a group of formula (IA) as depicted above wherein:

5 X is -O-;

R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

Ring A is aryl;

10 R¹⁰ is carbamoyl or *N*-(C₁₋₁₀alkyl)carbamoyl or a group of formula (IB) (as depicted above) wherein R¹⁰ is optionally substituted on carbon by one or more substituents selected from R²³ and wherein:

R¹¹ is hydrogen;

R¹² and R¹³ are independently selected from hydrogen, carbamoyl or C₁₋₆alkyl;

15 wherein R¹² and R¹³ may be independently optionally substituted on carbon by one or more substituents selected from R²⁵;

R¹⁴ is selected from carbamoyl, hydroxyaminocarbonyl, C₁₋₆alkyl, carbocyclyl, heterocyclyl or carbocyclyl-(C₁₋₆alkylene)_p-R²⁷-(C₁₋₆alkylene)_q-; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²⁹; and wherein if
20 said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R³⁰; or R¹⁴ is a group of formula (IC) (as depicted above) wherein:

R¹⁵ is hydrogen;

R¹⁶ is C₁₋₆alkyl; wherein R¹⁶ may be optionally substituted on carbon by one or more groups selected from R³¹;

25 n is 1;

R²³ is hydroxy;

R²⁵, R²⁹ or R³¹ are independently selected from halo, hydroxy, amino, sulphamoyl, C₁₋₆alkoxy, *N,N,N*-(C₁₋₆alkyl)₃ammonio, *N,N*-(C₁₋₆alkyl)₂sulphamoylamino, C₁₋₆alkoxycarbonylamino, carbocyclyl, heterocyclyl,
30 carbocyclyl-(C₁₋₆alkylene)_p-R³²-(C₁₋₆alkylene)_q- or

heterocyclyl-(C₁₋₆alkylene)_r-R³³-(C₁₋₆alkylene)_s-; wherein R²⁵, R²⁹ or R³¹ may be independently optionally substituted on carbon by one or more R³⁴; and wherein if said

heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R³⁵;

R²⁷, R³² or R³³ are independently selected from -O-, -NR³⁶C(O)NR³⁶-, -OC(O)N=C- or -NR³⁶C(O)-; wherein R²³ is hydrogen;

5 p, q, r and s are independently selected from 0 or 1;

R³⁴ is selected from hydroxy, amino, carbamoyl, sulphamoyl or methoxy;

R³⁰ or R³⁵ are independently selected from C₁₋₆alkyl or C₁₋₆alkoxycarbonyl.

R⁵ is a group of formula (IA) as depicted above wherein:

X is -O-;

10 R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

Ring A is aryl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R¹⁸;

15 R¹⁰ is carbamoyl or N-(C₁₋₁₀alkyl)carbamoyl or a group of formula (IB) (as depicted above) wherein R¹⁰ is optionally substituted on carbon by one or more substituents selected from R²³ and wherein:

R¹¹ is hydrogen or C₁₋₆alkyl;

R¹² and R¹³ are independently selected from hydrogen, carbamoyl or C₁₋₆alkyl;

20 wherein R¹² and R¹³ may be independently optionally substituted on carbon by one or more substituents selected from R²⁵;

R¹⁴ is selected from carbamoyl, hydroxyaminocarbonyl, C₁₋₆alkyl, carbocyclyl, heterocyclyl or carbocyclyl-(C₁₋₆alkylene)_p-R²⁷-(C₁₋₆alkylene)_q-; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²⁹; and wherein if
25 said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R³⁰; or R¹⁴ is a group of formula (IC) (as depicted above) wherein:

R¹⁵ is hydrogen;

R¹⁶ is C₁₋₆alkyl; wherein R¹⁶ may be optionally substituted on carbon by one or more groups selected from R³¹;

30 n is 1;

R¹⁸ is hydroxy;

R²³ is hydroxy;

R^{25} , R^{29} or R^{31} are independently selected from halo, hydroxy, amino, sulphamoyl, amidino, C_{1-6} alkoxy, N,N,N -(C_{1-6} alkyl)₃ammonio, N,N -(C_{1-6} alkyl)₂sulphamoylamino, C_{1-6} alkoxycarbonylamino, carbocyclyl, heterocyclyl, carbocyclyl-(C_{1-6} alkylene)_p- R^{32} -(C_{1-6} alkylene)_q- or

- 5 heterocyclyl-(C_{1-6} alkylene)_r- R^{33} -(C_{1-6} alkylene)_s-; wherein R^{25} , R^{29} or R^{31} may be independently optionally substituted on carbon by one or more R^{34} ; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{35} ;

- 10 R^{27} , R^{32} or R^{33} are independently selected from -O-, -NR³⁶C(O)NR³⁶-, -OC(O)N=C- or -NR³⁶C(O)-; wherein R^{23} is hydrogen;

p, q, r and s are independently selected from 0 or 1;

R^{34} is selected from hydroxy, amino, carbamoyl, sulphamoyl or methoxy;

R^{30} or R^{35} are independently selected from C_{1-6} alkyl or C_{1-6} alkoxycarbonyl.

R^5 is a group of formula (IA) as depicted above wherein:

- 15 X is -O-;

R^7 is hydrogen;

R^8 is hydrogen;

R^9 is hydrogen;

Ring A is phenyl;

- 20 R^{10} is carbamoyl or a group of formula (IB) (as depicted above) wherein:

R^{11} is hydrogen;

R^{12} and R^{13} are independently selected from hydrogen, carbamoyl or C_{1-6} alkyl;

wherein R^{12} and R^{13} may be independently optionally substituted on carbon by one or more substituents selected from R^{25} ;

- 25 R^{14} is selected from carbamoyl, hydroxyaminocarbonyl, C_{1-6} alkyl, carbocyclyl, heterocyclyl or carbocyclyl-(C_{1-6} alkylene)_p- R^{27} -(C_{1-6} alkylene)_q-; wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{29} ; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{30} ; or R^{14} is a group of formula (IC) (as depicted above) wherein:

- 30 R^{15} is hydrogen;

R^{16} is C_{1-6} alkyl; wherein R^{16} may be optionally substituted on carbon by one or more groups selected from R^{31} ;

n is 1;

R^{25} , R^{29} or R^{31} are independently selected from halo, hydroxy, amino, sulphamoyl, C_{1-6} alkoxy, N,N,N -(C_{1-6} alkyl)₃ammonio, N,N -(C_{1-6} alkyl)₂sulphamoylamino, C_{1-6} alkoxycarbonylamino, carbocyclyl, heterocyclyl, carbocyclyl-(C_{1-6} alkylene)_p- R^{32} -(C_{1-6} alkylene)_q- or

- 5 heterocyclyl-(C_{1-6} alkylene)_r- R^{33} -(C_{1-6} alkylene)_s-; wherein R^{25} , R^{29} or R^{31} may be independently optionally substituted on carbon by one or more R^{34} ; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{35} ;

- 10 R^{27} , R^{32} or R^{33} are independently selected from -O-, -NR³⁶C(O)NR³⁶-, -OC(O)N=C- or -NR³⁶C(O)-; wherein R^{23} is hydrogen;

p, q, r and s are independently selected from 0 or 1;

R^{34} is selected from hydroxy, amino, carbamoyl, sulphamoyl or methoxy;

R^{30} or R^{35} are independently selected from C_{1-6} alkyl or C_{1-6} alkoxycarbonyl.

R^5 is a group of formula (IA) as depicted above wherein:

- 15 X is -O-;

R^7 is hydrogen;

R^8 is hydrogen;

R^9 is hydrogen;

- 20 Ring A is phenyl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R^{18} ;

R^{10} is carbamoyl or a group of formula (IB) (as depicted above) wherein:

R^{11} is hydrogen or C_{1-6} alkyl;

R^{12} and R^{13} are independently selected from hydrogen, carbamoyl or C_{1-6} alkyl;

- 25 wherein R^{12} and R^{13} may be independently optionally substituted on carbon by one or more substituents selected from R^{25} ;

R^{14} is selected from carbamoyl, hydroxyaminocarbonyl, C_{1-6} alkyl, carbocyclyl, heterocyclyl or carbocyclyl-(C_{1-6} alkylene)_p- R^{27} -(C_{1-6} alkylene)_q-; wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{29} ; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{30} ; or R^{14} is a group of formula (IC) (as depicted above) wherein:

- 30 R^{15} is hydrogen;

R^{16} is C_{1-6} alkyl; wherein R^{16} may be optionally substituted on carbon by one or more groups selected from R^{31} ;

R¹⁸ is hydroxy;

n is 1;

R²⁵, R²⁹ or R³¹ are independently selected from halo, hydroxy, amino, sulphamoyl, amidino, C₁₋₆alkoxy, *N,N,N*-(C₁₋₆alkyl)₃ammonio, *N,N*-(C₁₋₆alkyl)₂sulphamoylamino,

5 C₁₋₆alkoxycarbonylamino, carbocyclyl, heterocyclyl,

carbocyclyl-(C₁₋₆alkylene)_p-R³²-(C₁₋₆alkylene)_q- or

heterocyclyl-(C₁₋₆alkylene)_r-R³³-(C₁₋₆alkylene)_s-; wherein R²⁵, R²⁹ or R³¹ may be

independently optionally substituted on carbon by one or more R³⁴; and wherein if said

heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group

10 selected from R³⁵;

R²⁷, R³² or R³³ are independently selected from -O-, -NR³⁶C(O)NR³⁶-, -OC(O)N=C- or -NR³⁶C(O)-; wherein R²³ is hydrogen;

p, q, r and s are independently selected from 0 or 1;

R³⁴ is selected from hydroxy, amino, carbamoyl, sulphamoyl or methoxy;

15 R³⁰ or R³⁵ are independently selected from C₁₋₆alkyl or C₁₋₆alkoxycarbonyl.

R⁵ is a group of formula (IA) as depicted above wherein:

X is -O-;

R⁷ is hydrogen;

R⁸ is hydrogen;

20 R⁹ is hydrogen;

R¹⁰ is carbamoyl or a group of formula (IB) (as depicted above) wherein:

R¹¹ is hydrogen;

R¹² and R¹³ are independently selected from hydrogen, carbamoyl or methyl; wherein

R¹² and R¹³ may be independently optionally substituted on carbon by one or more

25 substituents selected from R²⁵;

R¹⁴ is selected from carbamoyl, hydroxyaminocarbonyl, methyl, ethyl, propyl, phenyl, 1,5-benzodioxepinyl, 2,3-dihydrobenzofuranyl, piperidinyl, anilinocarbonyl or

anilinocarbonyl; wherein R¹⁴ may be optionally substituted on carbon by one or more

substituents selected from R²⁹; and wherein said piperidinyl may be optionally substituted on

30 nitrogen by a group selected from R³⁰; or R¹⁴ is a group of formula (IC) (as depicted above)

wherein:

R¹⁵ is hydrogen;

R¹⁶ is methyl, ethyl or hexyl; wherein R¹⁶ may be optionally substituted on carbon by one or more groups selected from R³¹;

n is 1;

R²⁵, R²⁹ or R³¹ are independently selected from fluoro, hydroxy, amino, sulphamoyl, methoxy, *N,N,N*-trimethylamino, *N,N*-dimethylsulphamoylamino, *t*-butoxycarbonylamino, phenyl, morpholino, imidazolyl, indolyl, 2,4-thiazolidinedionyl, piperazinyl, 2-imidazolidinonyl, phenoxy, benzyloxycarbonyliminomethyl, *N*-pyridinylureido or *N*-pyrimidinylureido; wherein R²⁵, R²⁹ or R³¹ may be independently optionally substituted on carbon by one or more R³⁴; and wherein said imidazolyl, indolyl, piperazinyl or 2-imidazolidinonyl may be optionally substituted on nitrogen by a group selected from R³⁵;

R²⁷, R³² or R³³ are independently selected from -O-, -NHC(O)NH-, -OC(O)N=C- or -NHC(O)-;

p, q, r and s are independently selected from 0 or 1;

R³⁴ is selected from hydroxy, amino, carbamoyl, sulphamoyl or methoxy;

R³⁰ or R³⁵ are independently selected from methyl or C₁₋₆alkoxycarbonyl.

R⁵ is a group of formula (IA) as depicted above wherein:

X is -O-;

R⁷ is hydrogen;

R⁸ is hydrogen;

R⁹ is hydrogen;

Ring A is phenyl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R¹⁸;

R¹⁰ is carbamoyl or a group of formula (IB) (as depicted above) wherein:

R¹¹ is hydrogen or methyl;

R¹² and R¹³ are independently selected from hydrogen, carbamoyl or methyl; wherein R¹² and R¹³ may be independently optionally substituted on carbon by one or more substituents selected from R²⁵;

R¹⁴ is selected from carbamoyl, hydroxyaminocarbonyl, methyl, ethyl, propyl, phenyl, 1,5-benzodioxepinyl, 2,3-dihydrobenzofuranyl, piperidinyl, anilinocarbonyl or anilinocarbonyl; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²⁹; and wherein said piperidinyl may be optionally substituted on nitrogen by a group selected from R³⁰; or R¹⁴ is a group of formula (IC) (as depicted above) wherein:

R¹⁵ is hydrogen;

R¹⁶ is methyl, ethyl or hexyl; wherein R¹⁶ may be optionally substituted on carbon by one or more groups selected from R³¹;

n is 1;

5 R¹⁸ is hydroxy;

R²⁵, R²⁹ or R³¹ are independently selected from fluoro, hydroxy, amino, sulphamoyl, amidino, methoxy, *N,N,N*-trimethylamino, *N,N*-dimethylsulphamoylamino, *t*-butoxycarbonylamino, phenyl, morpholino, imidazolyl, indolyl, 2,4-thiazolidinedionyl, piperazinyl, 2-imidazolidinonyl, phenoxy, benzyloxycarbonyliminomethyl, *N'*-pyridinylureido or *N'*-pyrimidinylureido; wherein R²⁵, R²⁹ or R³¹ may be independently optionally substituted on carbon by one or more R³⁴; and wherein said imidazolyl, indolyl, piperazinyl or 2-imidazolidinonyl may be optionally substituted on nitrogen by a group selected from R³⁵;

R²⁷, R³² or R³³ are independently selected from -O-, -NHC(O)NH-, -OC(O)N=C- or -NHC(O)-;

15 p, q, r and s are independently selected from 0 or 1;

R³⁴ is selected from hydroxy, amino, carbamoyl, sulphamoyl or methoxy;

R³⁰ or R³⁵ are independently selected from methyl or C₁₋₆alkoxycarbonyl.

R⁵ is selected from:

N-{(R)-α-[*N*-(2-hydroxyethyl)carbamoyl]benzyl}carbamoylmethoxy;

20 *N*-{(R)-α-[*N*-(2-trimethylaminoethyl)carbamoyl]benzyl}carbamoylmethoxy;

N-{(R)-α-[*N*-(2-aminoethyl)carbamoyl]benzyl}carbamoylmethoxy;

N-{(R)-α-[*N*-(carbamoylmethyl)carbamoyl]benzyl}carbamoylmethoxy;

N-{(R)-α-[*N*-((S)-1-carbamoyl-2-hydroxyethyl)carbamoyl]benzyl}carbamoylmethoxy;

N-((R)-α-carbamoylbenzyl)carbamoylmethoxy;

25 *N*-{(R)-α-[*N*-(1,1-di-hydroxymethyl-2-hydroxyethyl)carbamoyl]benzyl}carbamoylmethoxy;

N-{(R)-α-[*N*-(hydroxycarbamoylmethyl)carbamoyl]benzyl}carbamoylmethoxy;

N-((R)-α-{*N*-[*N*-(2,2,2-trifluoroethyl)carbamoylmethyl]carbamoyl}benzyl)carbamoylmethoxy;

N-((R)-α-{*N*-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoylmethyl]

30 carbamoyl}benzyl)carbamoylmethoxy;

N-((R)-α-{*N*-[*N*-(2-fluoroethyl)carbamoylmethyl]carbamoyl}benzyl)carbamoylmethoxy;

N-((R)-α-{*N*-[*N*-(ethyl)carbamoylmethyl]carbamoyl}benzyl)carbamoylmethoxy;

- N*-((*R*)- α -{*N'*-[*N*-(4-hydroxy-3-methoxybenzyl)carbamoylmethyl]carbamoyl}benzyl)carbamoylmethoxy;
- N*-((*R*)- α -{*N'*-[*N*-(2-methoxyethyl)carbamoylmethyl]carbamoyl}benzyl)carbamoylmethoxy;
- N*-((*R*)- α -{*N'*-[*N*-(4-sulphamoylphenethyl)carbamoylmethyl]carbamoyl}benzyl)carbamoylmethoxy;
- 5 *N*-((*R*)- α -{*N'*-[*N*-(2-*N,N*-dimethylaminosulphamoyl)ethyl]carbamoylmethyl]carbamoyl}benzyl)carbamoylmethoxy;
- N*-[(*R*)- α -(*N'*-[*N*-(2-(*N'*-pyrimidin-2-ylureido)ethyl)carbamoylmethyl]carbamoyl)benzyl)carbamoylmethoxy;
- 10 (*N*-{(*R*)- α -[*N'*-(2-(*S*)-3-(*R*)-4-(*R*)-5-(*R*)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy;
- N*-{(*R*)- α -[*N'*-(3-morpholinopropyl)carbamoyl]benzyl}carbamoylmethoxy;
- N*-{(*R*)- α -[*N'*-(2-imidazol-4-ylethyl)carbamoyl]benzyl}carbamoylmethoxy;
- N*-{(*R*)- α -[*N'*-(2-*N,N*-dimethylaminosulphamoyl)ethyl]benzyl}carbamoylmethoxy;
- 15 *N*-((*R*)- α -{*N'*-[2-(2-hydroxyphenoxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy;
- N*-{(*R*)- α -[*N'*-(3-hydroxy-1,5-benzodioxepin-3-ylmethyl)carbamoyl]benzyl}carbamoylmethoxy;
- N*-{(*R*)- α -[*N'*-(3-*t*-butoxycarbonylaminobenzyl)carbamoyl]benzyl}carbamoylmethoxy;
- N*-((*R*)- α -{*N'*-[3-(benzyloxycarbonylimino-1-aminomethyl)benzyl]carbamoyl}benzyl)carbamoylmethoxy;
- 20 *N*-((*R*)- α -{*N'*-[2-(3,4-dihydroxyphenyl)-2-methoxyethyl]carbamoyl}benzyl)carbamoylmethoxy;
- N*-{(*R*)- α -[*N'*-(2,3-dihydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy;
- N*-((*R*)- α -{*N'*-[2-(5-methoxyindol-3-yl)ethyl]carbamoyl}benzyl)carbamoylmethoxy;
- 25 *N*-((*R*)- α -{*N'*-[2-(2,5-dioxothiazolidin-1-yl)ethyl]carbamoyl}benzyl)carbamoylmethoxy;
- N*-((*R*)- α -{*N'*-[3-(4-methylpiperazin-1-yl)propyl]carbamoyl}benzyl)carbamoylmethoxy;
- N*-{(*R*)- α -[*N'*-(4-sulphamoylphenethyl)carbamoyl]benzyl}carbamoylmethoxy;
- N*-{(*R*)- α -[*N'*-(5,6-dimethoxy-2,3-dihydrobenzofuran-2-ylmethyl)carbamoyl]benzyl}carbamoylmethoxy;
- 30 *N*-{(*R*)- α -[*N'*-(1-*t*-butoxycarbonylpiperidin-4-ylmethyl)carbamoyl]benzyl}carbamoylmethoxy;
- N*-{(*R*)- α -[*N'*-(4-nitroanilincarbonylmethyl)carbamoyl]benzyl}carbamoylmethoxy;

- N*-((R)- α -{*N*'-[2-(*N*'-pyrimidin-2-ylureido)ethyl]carbamoyl}benzyl)carbamoylmethoxy;
N-((R)- α -{*N*'-[2-(*N*'-pyridin-2-ylureido)ethyl]carbamoyl}benzyl)carbamoylmethoxy;
N-((R)- α -{*N*'-[2-(4-carbamoylphenoxy)ethyl]carbamoyl}benzyl)carbamoylmethoxy;
N-((R)- α -{*N*'-[2-(2-oxoimidazolidin-1-yl)ethyl]carbamoyl}benzyl)carbamoylmethoxy; and
 5 *N*-((R)- α -[*N*'-(3-aminobenzyl)carbamoyl]benzyl)carbamoylmethoxy.

R^5 is selected from:

- N*-((R)- α -[*N*'-(2-hydroxyethyl)carbamoyl]benzyl)carbamoylmethoxy;
N-((R)- α -[*N*'-(2-trimethylaminoethyl)carbamoyl]benzyl)carbamoylmethoxy;
N-((R)- α -[*N*'-(2-aminoethyl)carbamoyl]benzyl)carbamoylmethoxy;
 10 *N*-((R)- α -[*N*'-(carbamoylmethyl)carbamoyl]benzyl)carbamoylmethoxy;
N-((R)- α -[*N*'-((S)-1-carbamoyl-2-hydroxyethyl)carbamoyl]benzyl)carbamoylmethoxy;
N-((R)- α -carbamoylbenzyl)carbamoylmethoxy;
N-((R)- α -[*N*'-(1,1-di-hydroxymethyl-2-hydroxyethyl)carbamoyl]benzyl)carbamoylmethoxy;
N-((R)- α -[*N*'-(hydroxycarbamoylmethyl)carbamoyl]benzyl)carbamoylmethoxy;
 15 *N*-((R)- α -{*N*'-[*N*-(2,2,2-trifluoroethyl)carbamoylmethyl]carbamoyl}benzyl)
 carbamoylmethoxy;
N-((R)- α -{*N*'-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoylmethyl]
 carbamoyl}benzyl)carbamoylmethoxy;
N-((R)- α -{*N*'-[*N*-(2-fluoroethyl)carbamoylmethyl]carbamoyl}benzyl)carbamoylmethoxy;
 20 *N*-((R)- α -{*N*'-[*N*-(ethyl)carbamoylmethyl]carbamoyl}benzyl)carbamoylmethoxy;
N-((R)- α -{*N*'-[*N*-(4-hydroxy-3-methoxybenzyl)carbamoylmethyl]carbamoyl}benzyl)
 carbamoylmethoxy;
N-((R)- α -{*N*'-[*N*-(2-methoxyethyl)carbamoylmethyl]carbamoyl}benzyl)carbamoylmethoxy;
N-((R)- α -{*N*'-[*N*-(4-sulphamoylphenethyl)carbamoylmethyl]carbamoyl}benzyl)
 25 carbamoylmethoxy;
N-((R)- α -{*N*'-[*N*-(2-*N,N*-dimethylaminosulphamoyl)ethyl]carbamoylmethyl]carbamoyl}
 benzyl)carbamoylmethoxy;
N-((R)- α -{*N*'-[*N*-(2-(*N*'-pyrimidin-2-ylureido)ethyl)carbamoylmethyl]carbamoyl}benzyl)
 carbamoylmethoxy;
 30 (*N*-((R)- α -[*N*'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl)carba
 moylmethoxy;

- N*-{(R)- α -[*N*-(3-morpholinopropyl)carbamoyl]benzyl} carbamoylmethoxy;
N-{(R)- α -[*N*-(2-imidazol-4-ylethyl)carbamoyl]benzyl} carbamoylmethoxy;
N-{(R)- α -[*N*-(2-*N,N*-dimethylaminosulphamoyl)ethyl]carbamoyl]benzyl} carbamoylmethoxy;
N-{(R)- α -[*N*-(2-(2-hydroxyphenoxy)ethyl)carbamoyl]benzyl} carbamoylmethoxy;
5 *N*-{(R)- α -[*N*-(3-hydroxy-1,5-benzodioxepin-3-ylmethyl)carbamoyl]benzyl}
carbamoylmethoxy;
N-{(R)- α -[*N*-(3-*t*-butoxycarbonylaminobenzyl)carbamoyl]benzyl} carbamoylmethoxy;
N-{(R)- α -[*N*-(4-(*N*²-benzyloxycarbonylamidino)benzyl)carbamoyl]benzyl}
carbamoylmethoxy;
10 *N*-{(R)- α -[*N*-(2-(3,4-dihydroxyphenyl)-2-methoxyethyl)carbamoyl]benzyl}
carbamoylmethoxy;
N-{(R)- α -[*N*-(2,3-dihydroxypropyl)carbamoyl]benzyl} carbamoylmethoxy;
N-{(R)- α -[*N*-(2-(5-methoxyindol-3-yl)ethyl)carbamoyl]benzyl} carbamoylmethoxy;
N-{(R)- α -[*N*-(2-(2,5-dioxothiazolidin-1-yl)ethyl)carbamoyl]benzyl} carbamoylmethoxy;
15 *N*-{(R)- α -[*N*-(3-(4-methylpiperazin-1-yl)propyl)carbamoyl]benzyl} carbamoylmethoxy;
N-{(R)- α -[*N*-(4-sulphamoylphenethyl)carbamoyl]benzyl} carbamoylmethoxy;
N-{(R)- α -[*N*-(5,6-dimethoxy-2,3-dihydrobenzofuran-2-ylmethyl)carbamoyl]benzyl}
carbamoylmethoxy;
N-{(R)- α -[*N*-(1-*t*-butoxycarbonylpiperidin-4-ylmethyl)carbamoyl]benzyl}
20 carbamoylmethoxy;
N-{(R)- α -[*N*-(4-nitroanilincarbonylmethyl)carbamoyl]benzyl} carbamoylmethoxy;
N-{(R)- α -[*N*-(2-(*N*-pyrimidin-2-ylureido)ethyl)carbamoyl]benzyl} carbamoylmethoxy;
N-{(R)- α -[*N*-(2-(*N*-pyridin-2-ylureido)ethyl)carbamoyl]benzyl} carbamoylmethoxy;
N-{(R)- α -[*N*-(2-(4-carbamoylphenoxy)ethyl)carbamoyl]benzyl} carbamoylmethoxy;
25 *N*-{(R)- α -[*N*-(2-(2-oxoimidazolidin-1-yl)ethyl)carbamoyl]benzyl} carbamoylmethoxy;
N-{(R)- α -[*N*-(3-aminobenzyl)carbamoyl]benzyl} carbamoylmethoxy;
N-{(R)- α -[*N*-(piperidin-4-ylmethyl)carbamoyl]benzyl} carbamoylmethoxy;
N-{(R)- α -[*N*-(4-amidinobenzyl)carbamoyl]benzyl} carbamoylmethoxy; and
(*N*-{(R)- α -[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)-*N*'-methylcarbamoyl]-
30 4-hydroxybenzyl} carbamoylmethoxy.

Ring A is aryl.

Ring A is phenyl.

X is -O-.

Therefore in another aspect of the invention there is provided a compound of formula

(I) (as depicted above) wherein:

5 R^1 and R^2 are independently selected from C_{1-4} alkyl;

v is 0;

R^3 and R^6 are hydrogen;

R^4 is methylthio;

R^5 is a group of formula (IA) as depicted above wherein:

10 X is -O-;

R^7 is hydrogen;

R^8 is hydrogen;

R^9 is hydrogen;

Ring A is aryl;

15 R^{10} is carbamoyl or *N*-(C_{1-10} alkyl)carbamoyl or a group of formula (IB) (as depicted above) wherein R^{10} is optionally substituted on carbon by one or more substituents selected from R^{23} and wherein:

R^{11} is hydrogen;

R^{12} and R^{13} are independently selected from hydrogen, carbamoyl or C_{1-6} alkyl;

20 wherein R^{12} and R^{13} may be independently optionally substituted on carbon by one or more substituents selected from R^{25} ;

R^{14} is selected from carbamoyl, hydroxyaminocarbonyl, C_{1-6} alkyl, carbocyclyl, heterocyclyl or carbocyclyl-(C_{1-6} alkylene)_p- R^{27} -(C_{1-6} alkylene)_q-; wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{29} ; and wherein if
25 said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{30} ; or R^{14} is a group of formula (IC) (as depicted above) wherein:

R^{15} is hydrogen;

R^{16} is C_{1-6} alkyl; wherein R^{16} may be optionally substituted on carbon by one or more groups selected from R^{31} ;

30 n is 1;

R^{23} is hydroxy;

R^{25} , R^{29} or R^{31} are independently selected from halo, hydroxy, amino, sulphamoyl, C_{1-6} alkoxy, N,N,N -(C_{1-6} alkyl)₃ammonio, N,N -(C_{1-6} alkyl)₂sulphamoylamino, C_{1-6} alkoxycarbonylamino, carbocyclyl, heterocyclyl, carbocyclyl-(C_{1-6} alkylene)_p- R^{32} -(C_{1-6} alkylene)_q- or

- 5 heterocyclyl-(C_{1-6} alkylene)_r- R^{33} -(C_{1-6} alkylene)_s-; wherein R^{25} , R^{29} or R^{31} may be independently optionally substituted on carbon by one or more R^{34} ; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{35} ;

- 10 R^{27} , R^{32} or R^{33} are independently selected from -O-, -NR³⁶C(O)NR³⁶-, -OC(O)N=C- or -NR³⁶C(O)-; wherein R^{23} is hydrogen;

p, q, r and s are independently selected from 0 or 1;

R^{34} is selected from hydroxy, amino, carbamoyl, sulphamoyl or methoxy;

R^{30} or R^{35} are independently selected from C_{1-6} alkyl or C_{1-6} alkoxycarbonyl;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

- 15 Therefore in another aspect of the invention there is provided a compound of formula **(I)** (as depicted above) wherein:

R^v and R^w are both hydrogen;

One of R^1 and R^2 is ethyl and the other is butyl or R^1 and R^2 are both butyl;

R^x and R^y are both hydrogen;

- 20 v is 0;

R^3 and R^6 are hydrogen;

R^4 is hydrogen or methylthio;

R^5 is a group of formula **(IA)** as depicted above wherein:

X is -O-;

- 25 R^7 is hydrogen;

R^8 is hydrogen;

R^9 is hydrogen;

Ring A is aryl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R^{18} ;

- 30 R^{10} is carbamoyl or N -(C_{1-10} alkyl)carbamoyl or a group of formula **(IB)** (as depicted above) wherein R^{10} is optionally substituted on carbon by one or more substituents selected from R^{23} and wherein:

R^{11} is hydrogen or C_{1-6} alkyl;

R^{12} and R^{13} are independently selected from hydrogen, carbamoyl or C_{1-6} alkyl; wherein R^{12} and R^{13} may be independently optionally substituted on carbon by one or more substituents selected from R^{25} ;

R^{14} is selected from carbamoyl, hydroxyaminocarbonyl, C_{1-6} alkyl, carbocyclyl, heterocyclyl or carbocyclyl- $(C_{1-6}$ alkylene)_p- R^{27} -(C_{1-6} alkylene)_q-; wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{29} ; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{30} ; or R^{14} is a group of formula (IC) (as depicted above) wherein:

R^{15} is hydrogen;

R^{16} is C_{1-6} alkyl; wherein R^{16} may be optionally substituted on carbon by one or more groups selected from R^{31} ;

n is 1;

R^{18} is hydroxy;

R^{23} is hydroxy;

R^{25} , R^{29} or R^{31} are independently selected from halo, hydroxy, amino, sulphamoyl, amidino, C_{1-6} alkoxy, *N,N,N*-(C_{1-6} alkyl)₃ammonio, *N,N*-(C_{1-6} alkyl)₂sulphamoylamino, C_{1-6} alkoxycarbonylamino, carbocyclyl, heterocyclyl, carbocyclyl- $(C_{1-6}$ alkylene)_p- R^{32} -(C_{1-6} alkylene)_q- or heterocyclyl- $(C_{1-6}$ alkylene)_r- R^{33} -(C_{1-6} alkylene)_s-; wherein R^{25} , R^{29} or R^{31} may be independently optionally substituted on carbon by one or more R^{34} ; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{35} ;

R^{27} , R^{32} or R^{33} are independently selected from -O-, - $NR^{36}C(O)NR^{36}$ -, -OC(O)N=C- or - $NR^{36}C(O)$ -; wherein R^{23} is hydrogen;

p, q, r and s are independently selected from 0 or 1;

R^{34} is selected from hydroxy, amino, carbamoyl, sulphamoyl or methoxy;

R^{30} or R^{35} are independently selected from C_{1-6} alkyl or C_{1-6} alkoxycarbonyl.

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

In another aspect of the invention, preferred compounds of the invention are any one of the examples or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

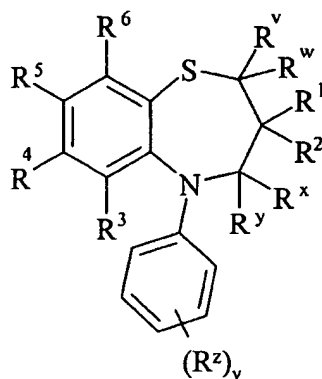
In a further aspect of the invention, preferred compounds of the invention are Examples 3, 5, 8, 18, 19, 22, 27, 28, 34, 36, 37 or 41 or a pharmaceutically acceptable salt,

solvate, solvate of such a salt or a prodrug thereof.

Preferred aspects of the invention are those which relate to the compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula (I)) comprises of:

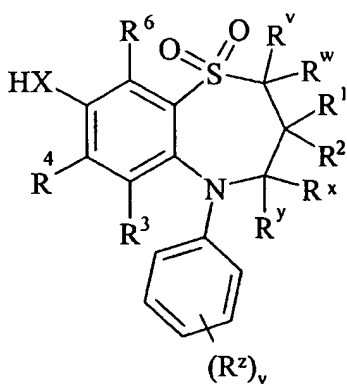
Process 1): oxidising a benzothiazepine of formula (II):



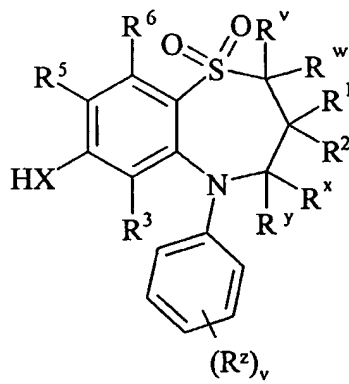
10

(II);

Process 2): for compounds of formula (I) wherein X is -O-, -NR^a or -S-; reacting a compound of formula (IIIa) or (IIIb):



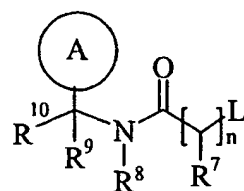
(IIIa)



(IIIb)

15 with a compound of formula (IV):

- 29 -

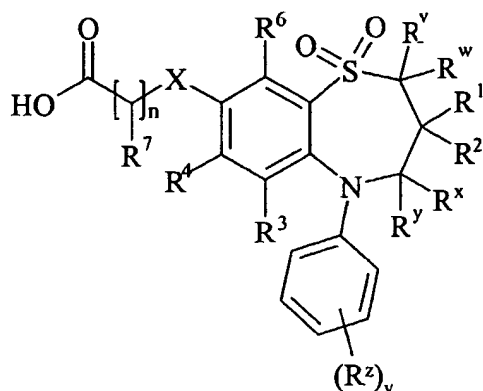


(IV)

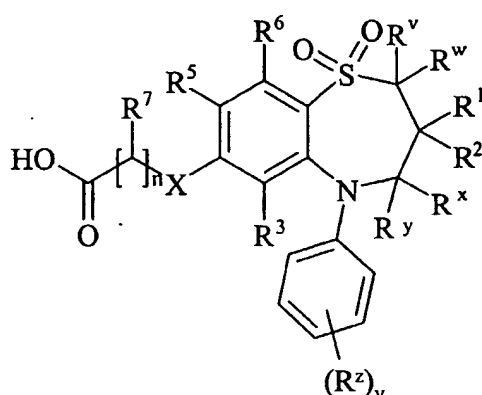
wherein L is a displaceable group;

Process 3): reacting an acid of formula (Va) or (Vb):

5

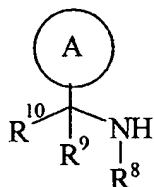


(Va)



(Vb)

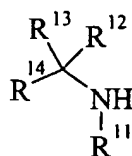
or an activated derivative thereof; with an amine of formula (VI):



(VI);

10

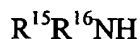
Process 4): for compounds of formula (I) wherein R¹⁰ is a group of formula (IB); reacting a compound of formula (I) wherein R¹⁰ is carboxy with an amine of formula (VII):



(VII)

15 *Process 5):* for compounds of formula (I) wherein R¹⁰ is a group of formula (IB) and R¹⁴ is a group of formula (IC) reacting a compound of formula (I) wherein R¹⁴ is carboxy with an amine of formula (VIII):

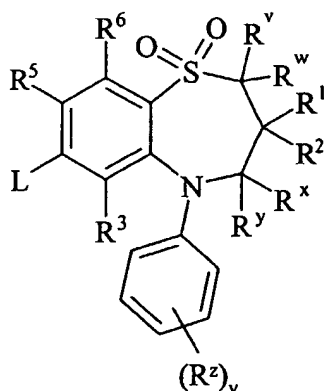
- 30 -



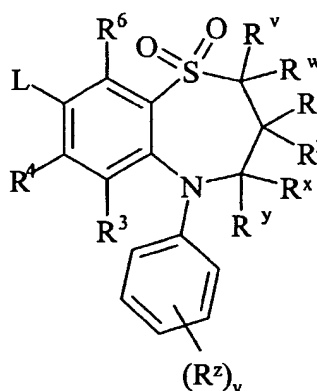
(VIII)

Process 6) for compounds of formula (I) wherein one of R^4 and R^5 are independently selected from C_{1-6} alkylthio optionally substituted on carbon by one or more R^{17} ; reacting a compound

5 of formula (IXa) or (IXb):



(IXa)



(IXb)

wherein L is a displaceable group; with a thiol of formula (X):



(X)

wherein R^y is C_{1-6} alkylthio optionally substituted on carbon by one or more R^{16} ;

and thereafter if necessary or desirable:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

15 iii) forming a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug.

L is a displaceable group, suitable values for L are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

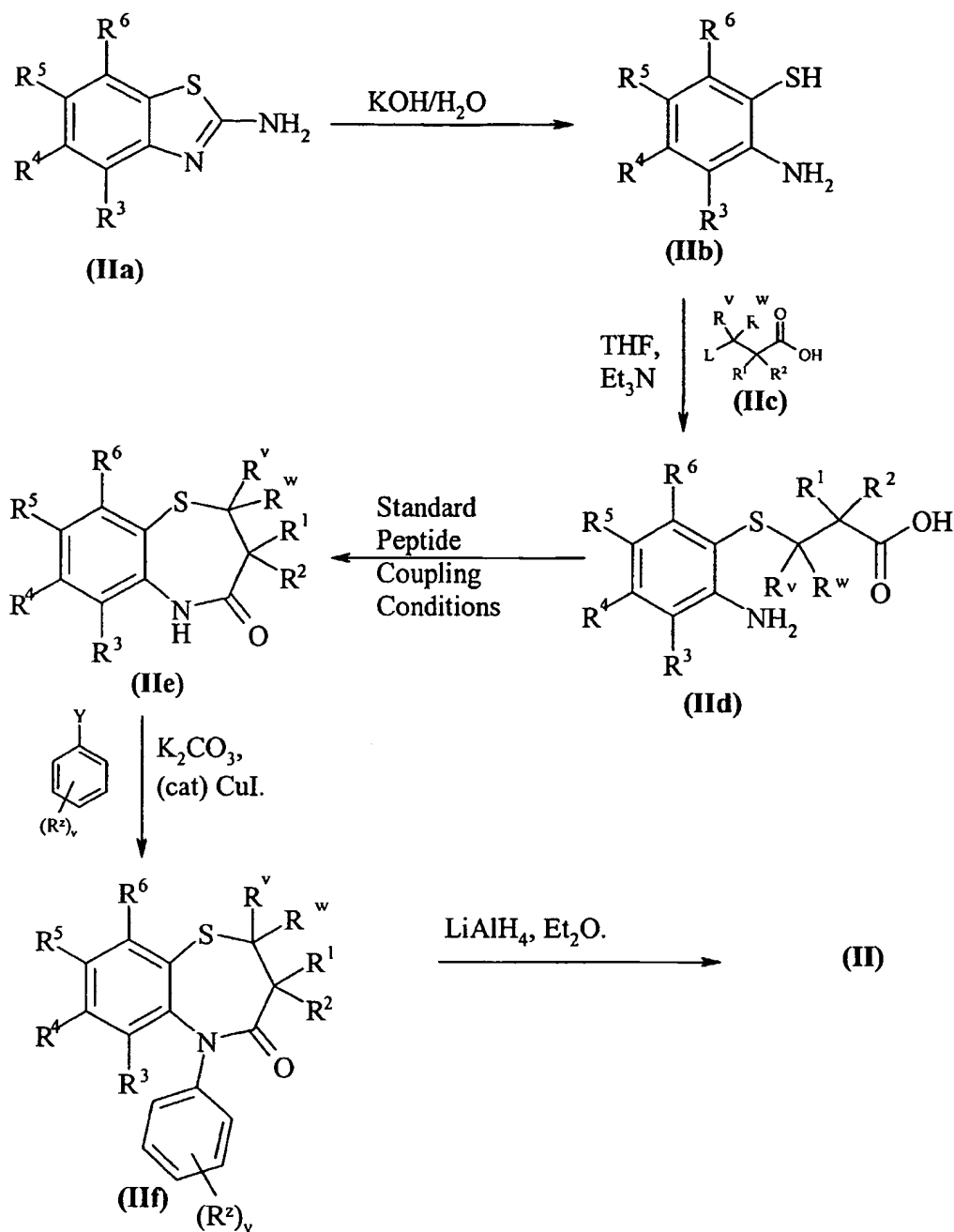
R^x is C_{1-6} alkyl. Preferably R^x is methyl or ethyl. More preferably R^x is methyl.

20 Specific reaction conditions for the above reactions are as follows.

Process 1): Benzothiazepines of formula (II) may be oxidised under standard sulphur oxidation conditions; for example using hydrogen peroxide and trifluoroacetic acid at a temperature in the range of 0°C to reflux, preferably at or near room temperature.

Compounds of formula (II) may be prepared according to Scheme I for compounds of
25 formula (I) wherein R^x and R^y are hydrogen. The skilled person will appreciate that where R^x

and R^y are not both hydrogen the following synthetic route needs to be manipulated using procedures known to the skilled person:



Scheme 1

- 5 wherein L is a displaceable group as defined above, and Y is a displaceable group, for example halo.

Compounds of formula **(IIa)** and **(IIc)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process 2): Compounds of formula (IIIa) or (IIIb) may be reacted with compounds of formula (IV) in the presence of a base for example an inorganic base such as sodium carbonate, or an organic base such as Hunigs base, in the presence of a suitable solvent such as acetonitrile, dichloromethane or tetrahydrofuran at a temperature in the range of 0°C to reflux, preferably at or near reflux.

Compounds of formula (IIIa) or (IIIb) may be prepared in a similar manner to compounds of formula (II) (but wherein R⁴ or R⁵ is -OH, -NH(R^a) or -SH followed by the oxidation step of Process 1).

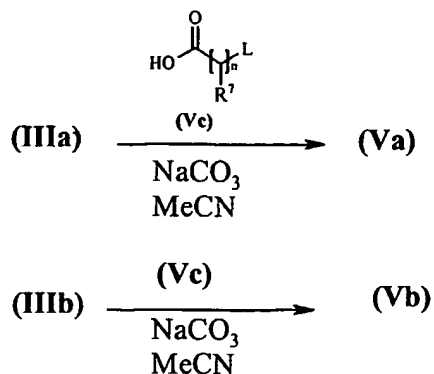
Compounds of formula (IV) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process 3) and Process 4) and Process 5): Acids and amines may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, or for example carbonyldiimidazole and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

Suitable activated acid derivatives include acid halides, for example acid chlorides, and active esters, for example pentafluorophenyl esters. The reaction of these types of compounds with amines is well known in the art, for example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

Compounds of formula (Va) or (Vb) wherein X=O-, -NR^a-, -S- may be prepared according to Scheme 2:

- 33 -

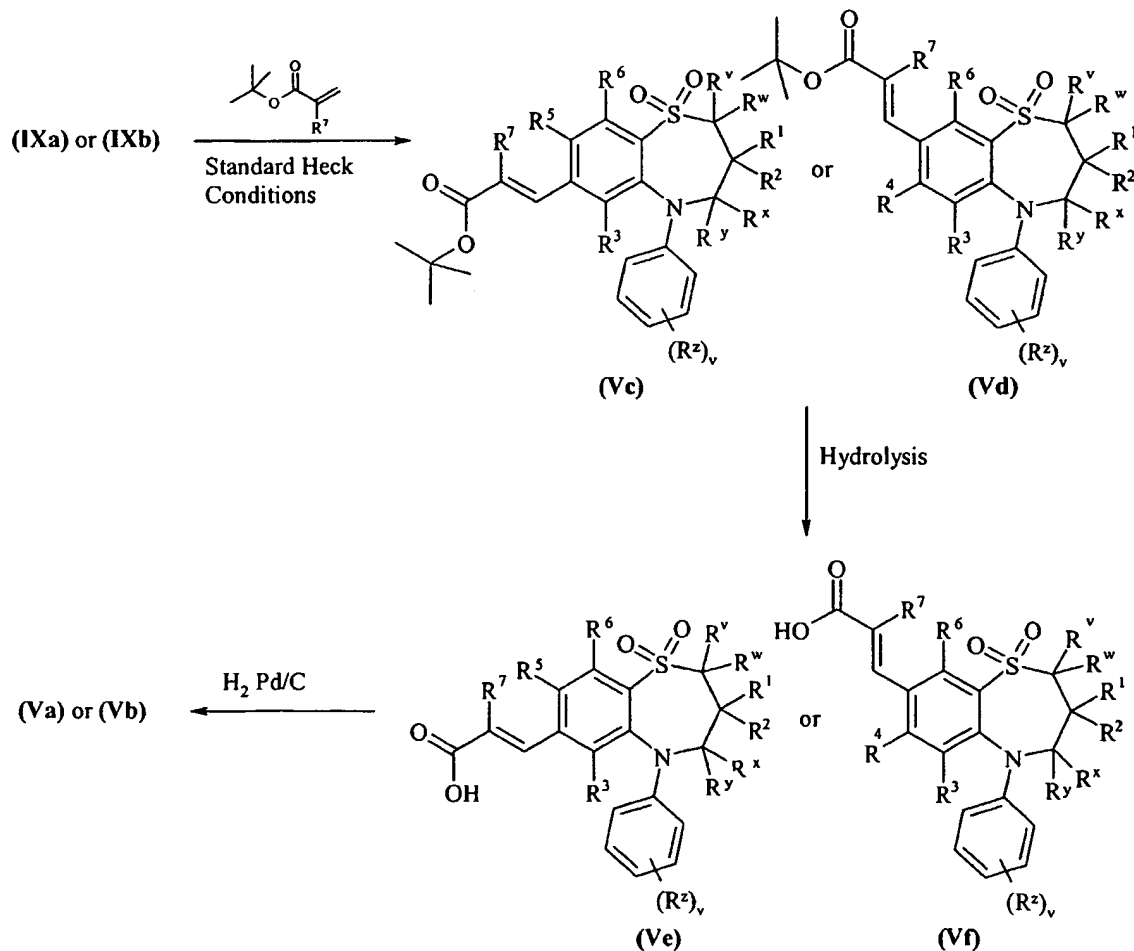


Scheme 2

wherein L is a displaceable group as defined above.

Compounds of formula (Va) and (Vb) where X is -SO- or -SO₂- may be prepared by
 5 oxidising the resulting compounds of formula (Va) and (Vb) from Scheme 2 where X is -S-.

Compounds of formula (Va) or (Vb) wherein X is -CH₂- may be prepared according to Scheme 3.



Scheme 3

Compounds of formula (Vc), (VI), (VII) and (VIII) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process 6): Compounds of formula (IXa) and (IXb) may be reacted with thiols of formula (X) in the presence of base, for example an inorganic base such as sodium carbonate or an organic base such as Hunigs base, in the presence of a suitable solvent such as DMF or THF at a temperature in the range of 0°C to reflux.

Compounds of formula (IXa) and (IXb) may be prepared by any of the procedures above for the preparation of compounds of formula (I), but wherein one of R⁴ and R⁵ is L.

Compounds of formula (X) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley

and Sons, 1999). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

As stated hereinbefore the compounds defined in the present invention possess IBAT inhibitory activity. These properties may be assessed, for example, using an *in vitro* test assay for studying the effect on bile acid uptake in IBAT-transfected cells (Smith L., Price-Jones M. J., Hugnes K. T. and Jones N. R. A.; J Biomolecular Screening, 3, 227-230) or *in vivo* by
5 studying the effect on radiolabelled bile acid absorption in mice/rats (Lewis M. C., Briecaddy L. E. and Root C., J., J Lip Res 1995, 36, 1098-1105).

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in association
10 with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

15 In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e.
20 approximately 0.1-100 mg/kg, preferably 0.02 -50 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg, particularly 0.1-10 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the
25 severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore for use in a method of prophylactic or therapeutic
30 treatment of a warm-blooded animal, such as man.

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, are effective IBAT inhibitors, and accordingly have value in the treatment of disease states

associated with hyperlipidaemic conditions.

Thus according to this aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore for use as a medicament.

5 According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore, in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

10 According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore, in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

15 According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

20 According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

Herein, where “the production of an IBAT inhibitory effect” or “producing an IBAT inhibitory effect” is referred to particularly this refers to the treatment of hyperlipidaemic conditions. In another aspect, “the production of an IBAT inhibitory effect” or “producing an IBAT inhibitory effect” refers to the treatment of dyslipidemic conditions and disorders such as hyperlipidaemia, hypertriglyceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia, hyperlipoproteinemia and hypoalphalipoproteinemia (low HDL). In another aspect “the production of an IBAT inhibitory effect” or “producing an IBAT inhibitory effect” refers to the treatment of different clinical conditions such as

30 atherosclerosis, arteriosclerosis, arrhythmia, hyper-thrombotic conditions, vascular dysfunction, endothelial dysfunction, heart failure, coronary heart diseases, cardiovascular diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, inflammation of

cardiovascular tissues such as heart, valves, vasculature, arteries and veins, aneurisms, stenosis, restenosis, vascular plaques, vascular fatty streaks, leukocytes, monocytes and/or macrophage infiltration, intimal thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks. In another aspect “the
5 production of an IBAT inhibitory effect” or “producing an IBAT inhibitory effect” refers to the treatment of atherosclerosis, coronary heart diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, stroke and transient ischaemic attacks in a warm-blooded animal, such as man.

According to a further feature of this aspect of the invention there is provided a
10 method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further feature of this aspect of the invention there is provided a
15 method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

The size of the dose required for the therapeutic or prophylactic treatment will
20 necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 0.1-50 mg/kg preferably 0.1-10 mg/kg is envisaged.

The IBAT inhibitory activity defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or
25 treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. According to this aspect of the invention there is provided a pharmaceutical product comprising a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as defined hereinbefore and an additional IBAT inhibitory substance as
30 defined hereinbefore and an additional hypolipidaemic agent for the conjoint treatment of hyperlipidaemia.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with an HMG Co-A reductase inhibitor, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable HMG Co-A reductase inhibitors, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are statins well known in the art. Particular statins are fluvastatin, lovastatin, pravastatin, simvastatin, atorvastatin, cerivastatin, bervastatin, dalvastatin, mevastatin and (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid (rosuvastatin), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A particular statin is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is atorvastatin calcium salt. A further particular statin is (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulphonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is rosuvastatin calcium salt.

In an additional aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof may be administered in association with an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and/or a bile acid binder thereby avoiding a possible risk of excess of bile acids in colon caused by the inhibition of the ileal bile acid transport system. An excess of bile acids in the visceral contents may cause diarrhoea. Thus, the present invention also provides a treatment of a possible side effect such as diarrhoea in patients during therapy comprising the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

An HMG CoA-reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof will by its action decrease the endogenous cholesterol available for the bile acid synthesis and have an additive effect in combination with the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof on lipid lowering.

Suitable bile acid binders for such a combination therapy are resins, such as cholestyramine and cholestipol. One advantage is that the dose of bile acid binder might be kept lower than the therapeutic dose for treatment of cholesterolaemia in single treatment

comprising solely a bile acid binder. By a low dose of bile acid binder any possible side effects caused by poor tolerance of the patient to the therapeutic dose could also be avoided.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with a bile acid binder.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in simultaneous, sequential or separate administration with a bile acid binder.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound

of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a bile acid binder.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in simultaneous, sequential or separate administration with a bile acid binder.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder.

According to a further aspect of the present invention there is provided a kit
5 comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof and a bile acid binder.

According to a further aspect of the present invention there is provided a kit
10 comprising:
a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and
15 c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:
a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
20 b) a bile acid binder; in a second unit dosage form; and
c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:
a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
25 b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form;
c) a bile acid binder; in a third unit dosage form; and
d) container means for containing said first, second and third dosage forms.

30 According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) a bile acid binder, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- c) a bile acid binder; in a third unit dosage form; and
- d) container means for containing said first, second and third dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder, in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder, in the manufacture
5 of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt,
10 solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, a bile acid binder, in the manufacture of a medicament for use in the
15 treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder, in the manufacture
20 of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof,
25 optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

30 According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof,

optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of a bile acid binder, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

5 According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of an HMG Co-A
10 reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable excipient, with the simultaneous, sequential or separate administration of an effective amount of a bile acid binder, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

15 According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents
20 selected from:

- a CETP (cholesteryl ester transfer protein) inhibitor, for example those referenced and described in WO 00/38725 page 7 line 22 - page 10, line 17 which are incorporated herein by reference;
- a cholesterol absorption antagonist for example azetidinones such as SCH 58235 and
25 those described in US 5,767,115 which are incorporated herein by reference;
- a MTP (microsomal transfer protein) inhibitor for example those described in Science, 282, 751-54, 1998 which are incorporated herein by reference;
- a fibric acid derivative; for example clofibrate, gemfibrozil, fenofibrate, ciprofibrate and bezafibrate;
- 30 ➤ a nicotinic acid derivative, for example, nicotinic acid (niacin), acipimox and niceritrol;
- a phytosterol compound for example stanols;
- probucol;

- an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);
- an antihypertensive compound for example an angiotensin converting enzyme inhibitor, an angiotensin II receptor antagonist, an adrenergic blocker, an alpha adrenergic blocker, a beta adrenergic blocker, a mixed alpha/beta adrenergic blocker, an adrenergic stimulant, calcium channel blocker, a diuretic or a vasodilator;
- insulin;
- sulphonylureas including glibenclamide, tolbutamide;
- metformin; and/or
- acarbose;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof, including active metabolites, which can be used in combination with a compound of formula (I) include but are not limited to, the following compounds: alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphan-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide,trandolapril,trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and enalaprilat. More preferred ACE inhibitors for uses in the present invention are ramipril and ramiprilat.

Preferred angiotensin II antagonists, pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof for use in combination with a compound of formula (I) include, but are not limited to, compounds: candesartan, candesartan cilexetil, losartan,

valsartan, irbesartan, tasosartan, telmisartan and eprosartan. Particularly preferred angiotensin II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil.

In another aspect of the invention, the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (in particular the compounds described in the patent applications listed on page 634) and J Med Chem, 2000, 43, 527 which are all incorporated herein by reference. Particularly a PPAR alpha and/or gamma agonist refers to WY-14643, clofibrate, fenofibrate, bezafibrate, GW 9578, troglitazone, pioglitazone, rosiglitazone, eglitazone, proglitazone, BRL-49634, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041, NN622/Ragaglitazar, BMS 298585 and GW 2433. Particularly a PPAR alpha and/or gamma agonist refers to (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxyphenyl}ethoxy)phenyl]propanoic acid and pharmaceutically acceptable salts thereof.

Therefore in an additional feature of the invention, there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
- b) a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt,

solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

In addition to their use in therapeutic medicine, the compounds of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of IBAT in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

Many of the intermediates described herein are novel and are thus provided as a further feature of the invention.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and particular embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated in the following non limiting examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these examples may be used where appropriate, and in which, unless otherwise stated:

- (i) evaporations were carried out by rotary evaporation *in vacuo* and work up procedures were carried out after removal of residual solids such as drying agents by filtration;
- (ii) all reactions were carried out under an inert atmosphere at ambient temperature, typically in the range 18-25°C, with solvents of HPLC grade under anhydrous conditions, unless otherwise stated;
- (iii) column chromatography (by the flash procedure) was performed on Silica gel 40-63 µm (Merck);
- (iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structures of the end products of the formula (I) were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; magnetic resonance chemical shift values were measured in deuterated CD₃OD (unless otherwise stated) on the delta scale (ppm downfield from tetramethylsilane); proton data is quoted unless
5 otherwise stated; spectra were recorded on a Varian Mercury-300 MHz, Varian Unity plus-400 MHz, Varian Unity plus-600 MHz or on Varian Inova-500 MHz spectrometer; and peak multiplicities are shown as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; tt, triple triplet; q, quartet; tq, triple quartet; m, multiplet; br, broad; LCMS were recorded on a Waters ZMD, LC column xTerra MS C₈(Waters), detection with a HP 1100 MS-detector
10 diode array equipped; mass spectra (MS) (loop) were recorded on VG Platform II (Fisons Instruments) with a HP-1100 MS-detector diode array equipped; unless otherwise stated the mass ion quoted is (MH⁺);

(vi) unless further details are specified in the text, analytical high performance liquid chromatography (HPLC) was performed on Prep LC 2000 (Waters), Kromasil C₈, 7μm, (Akzo
15 Nobel); MeCN and de-ionised water 100 mM ammonium acetate as mobile phases, with suitable composition;

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), HPLC, infra-red (IR), MS or NMR analysis;

(viii) where solutions were dried sodium sulphate was the drying agent;

(ix) where an "ISOLUTE" column is referred to, this means a column containing 2 g of silica, the silica being contained in a 6 ml disposable syringe and supported by a porous disc of 54Å pore size, obtained from International Sorbent Technology under the name "ISOLUTE";
20 "ISOLUTE" is a registered trade mark;

(x) the following abbreviations may be used hereinbefore or hereinafter:-

25	DCM	dichloromethane;
	DMF	N,N-dimethylformamide;
	TBTU	o-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate;
	EtOAc	ethyl acetate;
	MeCN	acetonitrile;
30	TFA	trifluoroacetic acid;
	HATU	o-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro-phosphate; and

DIPEA di-isopropylethylamine.

Example 1

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)- α -[N-(2-hydroxyethyl)
5 carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)- α -carboxybenzyl}
carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1; 50 mg, 0.082 mmol)
and 2-aminoethanol (18 μ l, 0.3 mmol) were dissolved in DCM (5 ml). The solution was
cooled to 0°C and TBTU (32 mg, 0.1 mmol) was added. The mixture was stirred for 15 min at
10 room temperature. An additional amount of 2-aminoethanol (100 μ l, 1.65 mmol), TBTU (90
mg, 0.28 mmol) and DMF (2 ml) were added. The reaction mixture was stirred over night at
room temperature. The solvents were evaporated under reduced pressure and the residue was
purified by preparative HPLC using MeCN/ammonium acetate buffer (60:40) as eluent. The
collected fractions were lyophilised to obtain 7 mg (13%) of the title compound. NMR (300
15 MHz): 0.7-0.9 (m, 6H), 1.0-1.25 (m, 4H), 1.4-1.65 (m, 4H), 2.15 (s, 3H), 3.2 (s, 2H), 3.5-8.85
(m, 4H), 4.6- 4.8 (m, 2H), 5.5 (s, 1H), 6.75 (s, 1H), 6.95-7.5 (m, 11H).

Example 2

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)- α -[N-(2-trimethylaminoethyl)
20 carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine acetate salt

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)- α -carboxybenzyl}
carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1; 50 mg, 0.082 mmol),
(2-aminoethyl)trimethylammonium chloride hydrochloride (57 mg, 0.33 mmol) and
triethylamine were added to DCM (5 ml) and DMF (1 ml). TBTU (42 mg, 0.13 mmol) was
25 added and the mixture was stirred at room temperature for 1 h. The solvents were evaporated
under reduced pressure and the residue was purified by preparative HPLC using
MeCN/ammonium acetate buffer (65:35) as eluent. The collected fractions were lyophilised to
obtain 8 mg (13%) of the title compound. NMR (300 MHz): 0.7-0.9 (m, 6H), 1.0-1.3 (m, 4H),
1.4-1.65 (m, 4H), 1.95 (s, 3H), 2.2 (s, 3H), 3.1 (s, 9H), 3.3 (s, 2H), 3.45-3.5 (m, 2H), 3.55-3.8
30 (m, 4H), 4.75 (s, 1H), 5.4 (s, 1H), 6.75 (s, 1H), 6.95-7.5 (m, 11H).

Example 3

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-(2-aminoethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine acetic acid salt

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -carboxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1; 50 mg, 0.082 mmol) and *t*-butyl *N*-(2-aminoethyl)carbamate (40 mg, 0.25 mmol) were added to DCM (5 ml). TBTU (42 mg, 0.13 mmol) was added and the reaction mixture was stirred for 2 hours at room temperature. TFA (1 ml) was added and the mixture was stirred for 1 hour at room temperature. The solvents were evaporated under reduced pressure and the residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (60:40) as eluent. The collected fractions were lyophilised to obtain 8 mg (13%) of the title compound. NMR (300 MHz): 0.7-0.9 (m, 6H), 1.0-1.25 (m, 4H), 1.35-1.65 (m, 4H), 1.9 (s, 3H), 2.15 (s, 3H), 2.95-3.1 (m, 4H), 3.25 (s, 2H), 3.5-3.85 (m, 4H), 4.75 (s, 2H), 5.45 (s, 1H), 6.7 (s, 1H), 6.95-7.5 (m, 11H).

Example 4

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N*-(carbamoylmethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -carboxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1; 50 mg, 0.082 mmol), glycineamide hydrochloride (27 mg, 0.24 mmol) and *N*-methylmorpholine (44 μ l, 0.4 mmol) were added to DCM (4 ml). TBTU (42 mg, 0.13 mmol) was added and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure and the residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (55:45) as eluent. The collected fractions were lyophilised to obtain 7 mg (13%) of the title compound. NMR (300 MHz): 0.7-0.9 (m, 6H), 1.0-1.3 (m, 4H), 1.4-1.65 (m, 4H), 3.25 (s, 2H), 3.7-4.0 (m, 3H), 4.7-4.8 (m, 2H), 5.5 (s, 1H), 6.7 (s, 1H), 6.95-7.5 (m, 11H).

Example 5

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)- α -[N'-((S)-1-carbamoyl-2-hydroxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)- α -carboxybenzyl}
5 carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1; 50 mg, 0.082 mmol),
L-serinamide hydrochloride (35 mg, 0.25 mmol) and N-methylmorpholine (44 μ l, 0.4 mmol)
were added to DCM (4 ml) and DMF (1 ml). TBTU (42 mg, 0.13 mmol) was added and the
mixture was stirred at room temperature for 2 hours. The solvents were evaporated under
reduced pressure and the residue was purified by preparative HPLC using MeCN/ammonium
10 acetate buffer (60:40) as eluent. The collected fractions were lyophilised to obtain 5 mg (9%)
of the title compound. NMR (300 MHz): 0.7-0.9 (m, 6H), 1.0-1.35 (m, 4H), 1.4-1.65 (m, 4H),
2.15 (s, 3H), 3.25b (s, 2H), 3.6-3.9 (m, 4H), 4.35-4.5 (m, 1H), 4.7-4.8 (m, 2H), 5.6 (d, 1H),
6.7 (s, 1H), 6.95-7.55 (m, 11H).

Example 6

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[N-((R)- α -carbamoylbenzyl)
carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-
tetrahydro-1,5-benzothiazepine (Method 17; 50 mg, 0.1 mmol), D-phenylglycinamide (18 mg,
20 0.12 mmol) and 2,6-lutidine (58 μ l, 0.5 mmol) were added to DCM (3 ml). TBTU (42 mg,
0.13 mmol) was added and the reaction mixture was stirred for 3 hours at room temperature
The mixture was purified by column chromatography on silica gel using EtOAc as eluent. The
residue was dissolved in toluene and was evaporated under reduced pressure. The residue was
solved in MeCN/water (50/50) and the mixture was lyophilised to obtain 27 mg (42%) of the
25 title compound. NMR (300 MHz): 0.7-0.9 (m, 6H), 1.0-1.3 (m, 4H), 1.4-1.65 (m, 4H), 2.15 (s,
3H), 3.2 (s, 2H), 3.55-3.9 (m, 2H), 4.7 (ABq, 2H), 5.5 (s, 1H), 6.75 (s, 1H), 6.95-7.5 (m,
11H).

Example 7

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)- α -[N-(1,1-di-hydroxymethyl-2-hydroxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)- α -carboxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1; 50 mg, 0.082 mmol), tris(hydroxymethyl)aminomethane (30 mg, 0.25 mmol) and 2,6-lutidine (58 μ l, 0.5 mmol) were added to DCM (3 ml). TBTU (42 mg, 0.13 mmol) was added and the mixture was stirred for 4 hours at room temperature. The solvent was evaporated under reduced pressure and the residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (55:45) as eluent. The collected fractions were lyophilised to obtain 5 mg (9%) of the title compound. NMR (300 MHz): 0.7-0.9 (m, 6H), 1.0-1.3 (m, 4H), 1.4-1.65 (m, 4H), 2.15 (s, 3H), 3.25 (s, 2H), 3.6-3.8 (m, 7H), 4.7-4.8 (m, 2H), 5.6 (s, 1H), 6.7 (s, 1H), 6.95-7.5 (m, 11H).

Example 8

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)- α -[N-(hydroxycarbamoylmethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)- α -carboxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1; 50 mg, 0.082 mmol), glycine hydroxamic acid (22 mg, 0.24 mmol) and 2,6-lutidine (58 μ l, 0.5 mmol) were added to DCM (3 ml). TBTU (42 mg, 0.13 mmol) was added and the mixture was stirred for 3 hours at room temperature. The mixture was washed with water and the organic layer was dried and evaporated under reduced pressure. The residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (60:40) as eluent. The collected fractions were lyophilised to obtain 7 mg (13%) of the title compound. NMR (500 MHz): 0.7-0.9 (m, 6H), 0.95-1.3 (m, 4H), 1.4-1.7 (m, 4H), 2.15 (s, 3H), 3.25 (s, 2H), 3.7-3.95 (m, 4H), 4.6 (s, 2H), 5.5 (s, 1H), 6.7 (s, 1H), 6.95-7.55 (m, 11H).

Example 9

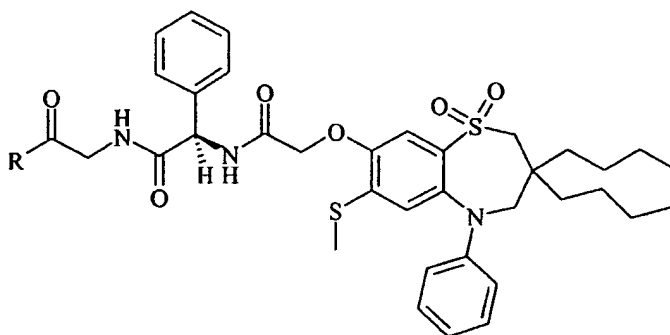
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -[N-(2,2,2-trifluoroethyl)carbamoylmethyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

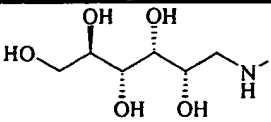
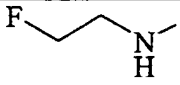

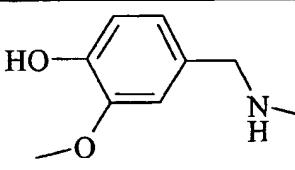
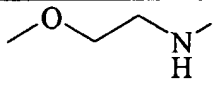
5 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)- α -[N'-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 6; 50 mg, 0.072 mmol), trifluoroethylamine (8.5 mg, 0.086 mmol) and TBTU (27 mg, 0.084 mmol) were dissolved in DCM and 2,6-lutidine (0.020 ml, 0.18 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours and was filtered through a short silica
10 column. The product was further purified with preparative HPLC (MeCN/ammonium acetate buffer (50:50→100:0)) to give the title compound (45 mg, 81 %). NMR (400 MHz, DMSO- d_6): 0.75 (m, 6 H), 0.95-1.46 (m, 12 H), 2.15 (s, 3 H), 3.28 (m, 2 H), 3.60-3.94 (m, 4 H), 4.73/4.84 (ABq, 2 H), 5.56 (d, 1 H), 6.67 (s, 1 H), 6.85 (t, 1 H), 6.99 (d, 2 H), 7.17-7.46 (8 H), 8.53 (t, 1 H), 8.61 (d, 1 H), 8.75 (t, 1 H).

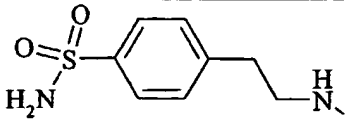
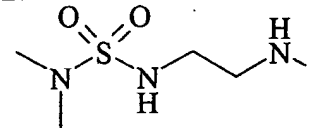
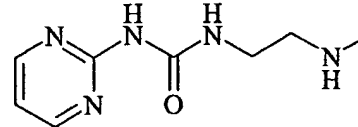
15

Examples 10-17

The following examples were prepared by the procedure of Example 9 using
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-((R)- α -[N'-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 6) and the
20 appropriate amine.



Ex	R	NMR 400 MHz, DMSO-d ₆
10 ¹		0.74 (m, 6H), 0.95-1.45 (m, 12H), 1.85 (s, 1H), 2.16 (s, 3H), 3.00 (m, 1H), 3.25-3.40 (br s, 5H), 3.45-3.85 (m, 4H), 4.72/4.84 (ABq, 2H), 5.60 (d, 1H), 5.75 (s, 1H), 6.65 (s, 1H), 6.86 (t, 1H), 6.98 (d, 2H), 7.17-7.46 (m, 8H), 7.76 (t, 1H), 8.58 (d, 1H), 8.66 (t, 1H)
11		0.74 (m, 6H), 0.96-1.48 (m, 12H), 2.15 (s, 3H), 3.28 (m, 1H), 3.64 (dd, 1H), 3.80 (dd, 1H), 4.33 (t, 1H), 4.45 (t, 1H), 4.73/4.84 (ABq, 2H), 5.55 (d, 1H), 6.67 (s, 1H), 6.86 (t, 1H), 6.99 (d, 2H), 7.18-7.46 (m, 8H), 8.08 (t, 1H), 8.61 (d, 1H), 8.70 (t, 1H)
12		0.74 (m, 6H), 0.97 (t, 3H), 0.95-1.48 (m, 12H), 2.15 (s, 3H), 3.05 (m, 2H), 3.24 (m, 2H), 3.65 (dq, 2H), 4.74/4.84 (ABq, 2H), 5.53 (d, 1H), 6.67 (s, 1H), 6.86 (t, 1H), 6.99 (d, 2H), 7.17-7.46 (m, 8H), 7.73 (t, 1H), 8.62 (d, 1H), 8.68 (t, 1H)
13		0.74 (m, 6H), 0.94-1.48 (m, 12H), 2.15 (s, 3H), 3.65-3.85 (m, 2H), 3.70 (s, 3H), 4.14 (t, 2H), 4.72/4.83 (ABq, 2H), 5.60 (d, 1H), 6.60-7.01 (m, 7H), 7.15-7.45 (m, 8H), 8.17 (t, 1H), 8.60 (d, 1H), 8.70 (t, 1H)
14		0.75 (m, 6H), 0.95-1.46 (m, 12H), 2.15 (s, 3H), 3.20 (s, 3H), 3.30 (t, 2H), 3.60 (dd, 1H), 3.76 (dd, 1H), 4.74/4.86 (ABq, 2H), 5.54 (d, 1H), 6.67 (s, 1H), 6.86 (t, 1H), 6.99 (d, 2H), 7.17-7.45 (m, 8H), 7.85 (t, 1H), 8.61 (d, 1H), 8.69 (t, 1H)

15 ¹		0.75 (m, 6H), 0.95-1.46 (m, 12H), 2.13 (s, 3H), 2.75 (t, 2H), 3.58 (dd, 1H), 3.74 (dd, 1H), 4.74/4.85 (ABq, 2H), 5.53 (d, 1H), 6.66 (s, 1H), 6.85 (t, 1H), 6.99 (d, 2H), 7.16-7.47 (m, 10H), 7.71 (m, 2H), 7.89 (t, 1H), 8.65 (d, 1H), 8.69 (t, 1H)
16 ¹		0.75 (m, 6H), 0.95-1.46 (m, 12H), 2.15 (s, 3H), 2.62 (s, 6H), 2.91 (m, 2H), 3.13 (m, 2H), 3.61 (dd, 1H), 3.76 (dd, 1H), 4.74/4.84 (ABq, 2H), 5.56 (d, 1H), 6.67 (s, 1H), 6.86 (t, 1H), 6.99 (d, 2H), 7.14-7.48 (m, 8H), 7.91 (t, 1H), 8.60 (d, 1H), 8.68 (t, 1H)
17 ¹		0.74 (m, 6H), 0.96-1.46 (m, 12H), 2.15 (s, 3H), 3.60 (m, 1H), 3.75 (m, 1H), 4.73/4.84 (ABq, 2H), 5.55 (d, 1H), 6.65 (s, 1H), 6.85 (t, 1H), 7.00-7.45 (m, 12H), 8.00 (t, 1H), 8.52 (d, 1H), 8.61 (m, 1H), 8.69 (t, 1H)

¹ DMF as solvent**Example 18**

- 5 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-α-[N'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl]carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-α-carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 8; 60 mg, 0.094 mmol) and 1-amino-1-deoxy-D-glucitol (20 mg, 0.11 mmol) were dissolved in DMF (2 ml) (40°C for a few minutes was required). 2,6-Dimethylpyridine (22 μl, 0.19 mmol) and HATU (43 mg, 0.111 mmol) were added at room temperature to the solution and the mixture was stirred for 30 minutes. The solvent was evaporated under reduced pressure and the product was purified by preparative HPLC using a MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as

15 eluent to give the title compound, 52 mg (69%). NMR (400 MHz): 0.77-0.85 (brt, 6H), 1.0-1.35 (m, 8H), 1.35-1.6 (m, 4H), 2.15 (s, 3H), 3.16-3.27 (m, 3H), 3.51 (dd, 1H) 3.54-3.86 (m, 8H), 4.70 (ABq, 2H), 5.52 (s, 1H), 6.70 (s, 1H), 6.98 (t, 1H), 7.11 (brd, 2H), 7.24-7.41 (m, 6H), 7.44 (brd, 2H); m/z 802.5.

Example 19

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)- α -[N-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

5 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)- α -carboxybenzyl}
carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1; 40 mg, 0.065 mmol),
1-amino-1-deoxy-D-glucitol (17 mg, 0.094 mmol) and DIPEA (55 μ l, 0.32 mmol) were
dissolved in DMF (2 ml) (40°C for a few minutes was required). TBTU (25 mg, 0.079 mmol)
was added at room temperature to the solution and the mixture was stirred over night. The
10 solvent was evaporated under reduced pressure and the product was purified by preparative
HPLC using an MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give the
title compound, 31 mg (61%). NMR (400 MHz): 0.75-0.90 (m, 6H), 1.0-1.35 (m, 4H),
1.35-1.7 (m, 4H), 2.15 (s, 3H), 3.17-3.27 (m, 3H), 3.46-3.96 (m, 9H), 4.70 (ABq, 2H), 5.52 (s,
1H), 6.71 (s, 1H), 6.97 (t, 1H), 7.09 (brd, 2H), 7.23-7.50 (m, 8H); m/z 774.4.

15

Example 20

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)- α -[N-(3-morpholinopropyl)
carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

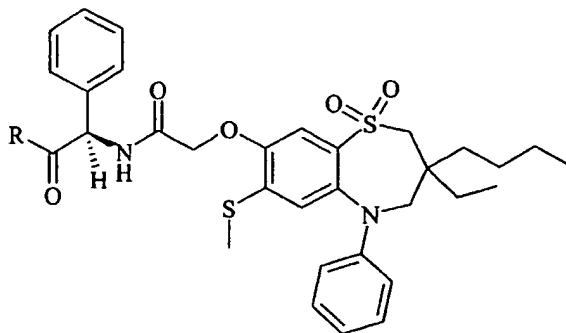
 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)- α -carboxybenzyl}
20 carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1; 40 mg, 0.065 mmol),
3-morpholinopropylamine (11 mg, 0.079 mmol) and N-methylmorpholine (14.4 μ l, 0.13
mmol) were dissolved in DCM (2 ml). HATU (34 mg, 0.089 mmol) was added and the
mixture was kept at room temperature over night. The product was purified using an
ISOLUTE column (Silica, 2 g) and eluted in 5 steps, 10 ml DCM, 10 ml DCM:EtOAc 8:2, 10
25 ml EtOAc, 10 ml EtOAc:MeOH (saturated with NH₃) and once again with 10 ml
EtOAc:MeOH (saturated with NH₃). The title compound was collected from the fourth step,
35 mg (72%). NMR (400 MHz): 0.74-0.90 (m, 6H), 1.0-1.35 (m, 4H), 1.35-1.7 (m, 4H),
1.76-1.9 (m, 2H), 2.15 (s, 3H), 2.65-3.04 (m, 6H), 3.24 (brs, 2H), 3.6-3.9 (m, 8H), 4.72 (ABq,
2H), 5.36 (s, 1H), 6.72 (s, 1H), 6.97 (t, 1H), 7.10 (brd, 2H), 7.23-7.50 (m, 8H); m/z 737.4.

30

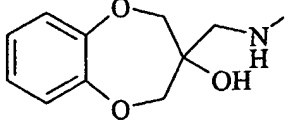
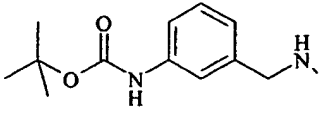
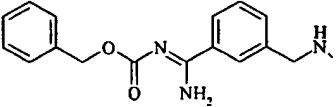
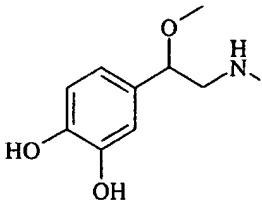
Examples 21-39

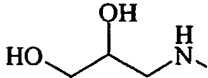
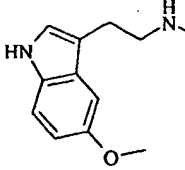
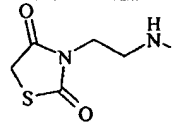
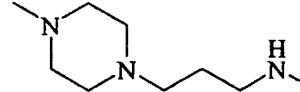
The following examples were prepared by the procedure of Example 20 using 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -carboxybenzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 1) and the appropriate

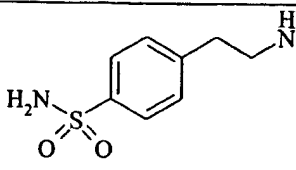
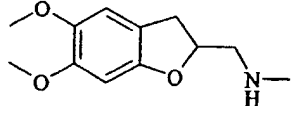
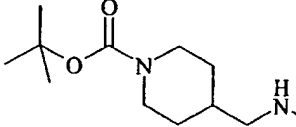
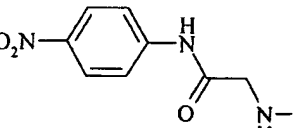
5 amine.

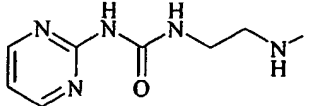
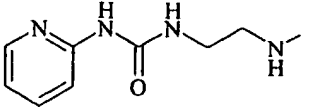
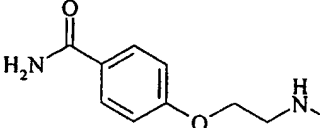
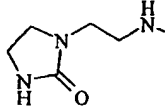


Ex	R	NMR 400 MHz	m/z
21		0.75-0.87 (m, 6H), 1.01-1.35 (m, 4H), 1.35-1.67 (m, 4H), 2.15 (s, 3H), 2.81 (t, 2H), 3.23 (brs, 2H), 3.40-3.53 (m, 2H), 3.60-3.86 (m, 2H), 4.70 (ABq, 2H), 5.38 (s, 1H), 6.71 (s, 1H), 6.85 (s, 1H), 6.97 (t, 1H), 7.09 (brd, 2H), 7.27 (t, 2H), 7.31-7.43 (m, 6H), 8.21 (s, 1H)	704.5
22		0.74-0.87 (m, 6H), 1.0-1.3 (m, 4H), 1.37-1.66 (m, 4H), 2.16 (s, 3H), 2.69 (s, 6H), 3.05-3.15 (m, 4H), 3.23 (brs, 2H), 3.55-3.9 (m, 2H), 4.70 (ABq, 2H), 5.47 (s, 1H), 6.71 (s, 1H), 6.97 (t, 1H), 7.09 (brd, 2H), 7.23-7.48 (m, 8H)	760.4
23		0.73-0.86 (m, 6H), 1.0-1.3 (m, 4H), 1.35-1.65 (m, 4H), 2.15 (s, 3H), 3.21 (brs, 2H), 3.54-3.9 (m, 4H), 3.94-4.06 (m, 2H), 4.69 (ABq, 2H), 5.51 (s, 1H), 6.68-6.85 (m, 5H), 6.96 (t, 1H), 7.09 (brd, 2H), 7.22-7.34 (m, 5H), 7.37-7.46 (m, 3H)	746.4

24		0.75-0.85 (m, 6H), 1.0-1.27 (m, 4H), 1.36-1.66 (m, 4H), 2.15 (s, 3H), 3.23 (brs, 2H), 3.45 (ABq, 2H), 3.6-4.05 (m, 6H), 4.70 (ABq, 2H), 5.54 (s, 1H), 6.71 (s, 1H), 6.86 (brs, 4H), 6.96 (t, 1H), 7.09 (brd, 2H), 7.23-7.37 (m, 5H), 7.40 (s, 1H), 7.45 (brd, 2H)	788.4
25		0.76-0.84 (m, 6H), 1.0-1.3 (m, 4H), 1.3-1.67 (m, 13H), 2.16 (s, 3H), 3.20 (brs, 2H), 3.58-3.9 (m, 2H), 4.34 (brs, 2H), 4.72 (ABq, 2H), 5.53 (s, 1H), 6.71 (s, 1H), 6.78 (d, 1H), 6.96 (t, 1H), 7.06-7.16 (m, 3H), 7.22-7.47 (m, 10H)	815.5
26		0.72-0.9 (m, 6H), 0.95-1.35 (m, 4H), 1.35-1.67 (m, 4H), 2.13 (s, 3H), 3.21 (brs, 2H), 3.57-3.9 (m, 2H), 4.46 (brs, 2H), 4.70 (ABq, 2H), 5.27 (brs, 2H), 5.51 (s, 1H), 6.68-6.73 (m, 1H), 6.96 (t, 1H), 7.05-7.15 (m, 2H), 7.20-7.54 (m, 15H), 7.68-7.79 (m, 2H)	876.4
27		(600 MHz, 1:1 diastereomeric mixture) 0.74-0.82 (m, 6H), 1.0-1.3 (m, 4H), 1.3-1.65 (m, 4H), 2.15 (s, 3H), 3.04 (s, 1.5H), 3.12 (s, 1.5H), 3.18-3.3 (m, 3H), 3.35-3.44 (m, 1H), 3.55-3.9 (m, 2H), 3.98 (dd, 0.5H), 4.04 (dd, 0.5H), 4.63-4.74 (m, 2H), 5.48 (s, 0.5H), 5.50 (s, 0.5H), 6.42 (dd, 0.5H), 6.55 (dd, 0.5H), 6.62 (d, 0.5H), 6.66-6.72 (m, 2.5H), 6.95 (t, 1H), 7.08 (brd, 2H), 7.23-7.40 (m, 8H)	774.5

28	 <chem>NCC(O)CS</chem>	(600 MHz) 0.75-0.83 (m, 6H), 1.0-1.3 (m, 4H), 1.35-1.63 (m, 4H), 2.15 (s, 3H), 3.14-3.44 (m, 6H), 3.59-3.88 (m, 3H), 4.69 (ABq, 2H), 5.50 (s, 1H), 6.70 (s, 1H), 6.95 (t, 1H), 7.08 (d, 2H), 7.24-7.32 (m, 3H), 7.34 (t, 2H), 7.39 (s, 1H), 7.43 (brd, 2H)	684.4
29	 <chem>NCCc1c[nH]c2cc(OC)ccc12</chem>	(600 MHz) 0.77 (brt, 6H), 0.95-1.28 (m, 4H), 1.33-1.60 (m, 4H), 2.14 (s, 3H), 2.77-2.89 (m, 2H), 3.18 (brs, 2H), 3.39-3.50 (m, 2H), 3.50-3.85 (m, 5H), 4.66 (ABq, 2H), 5.43 (s, 1H), 6.68-6.72 (m, 2H), 6.77 (s, 1H), 6.94 (t, 1H), 6.99 (d, 1H), 7.06 (brd, 2H), 7.16 (d, 1H), 7.2-7.36 (m, 7H), 7.38 (s, 1H)	783.4
30	 <chem>NCCN1C(=O)SCC1=O</chem>	(600 MHz) 0.75-0.85 (m, 6H), 1.0-1.27 (m, 4H), 1.38-1.63 (m, 4H), 2.17 (s, 3H), 3.22 (brs, 2H), 3.33-3.39 (m, 1H), 3.47-3.53 (m, 1H), 3.57-3.96 (m, 6H), 4.69 (ABq, 2H), 5.38 (s, 1H), 6.71 (s, 1H), 6.95 (t, 1H), 7.08 (brd, 2H), 7.23-7.40 (m, 8H)	753.5
31	 <chem>NCCN1CCN(CCCN)CC1</chem>	(600 MHz) 0.74-0.83 (m, 6H), 1.0-1.28 (m, 4H), 1.38-1.62 (m, 4H), 1.7 (m, 2H), 2.14 (s, 3H), 2.44-2.56 (m, 2H), 2.56-2.86 (m, 5H), 2.86-3.10 (m, 4H), 3.22 (brs, 2H), 3.25 (t, 2H), 3.57-3.87 (m, 4H), 4.69 (ABq, 2H), 5.38 (s, 1H), 6.70 (s, 1H), 6.96 (t, 1H), 7.08 (brd, 2H), 7.26 (t, 2H), 7.30-7.40 (m, 4H), 7.43 (d, 2H)	750.6

32		(600 MHz) 0.74-0.85 (m, 6H), 1.0-1.3 (m, 4H), 1.37-1.65 (m, 4H), 2.17 (s, 3H), 2.81 (t, 2H), 3.22 (brs, 2H), 3.32-3.41 (m, 1H), 3.50-3.59 (m, 1H), 3.6-3.85 (m, 2H), 4.68 (ABq, 2H), 5.40 (s, 1H), 6.72 (s, 1H), 6.97 (t, 1H), 7.09 (d, 2H), 7.17 (d, 2H), 7.27 (t, 2H), 7.31-7.37 (m, 5H), 7.39 (s, 1H), 7.69 (d, 2H)	793.5
33		(600 MHz, 1:1 diastereomeric mixture) 0.72-0.84 (m, 6H), 0.98-1.28 (m, 4H), 1.36-1.61 (m, 4H), 2.13-2.16 (m, 3H), 2.68 (dd, 0.5H), 2.82 (dd, 0.5H), 3.02-3.14 (m, 1H), 3.14-3.23 (m, 2H), 3.38-3.45 (m, 1H), 3.46-3.53 (m, 1H), 3.55-3.9 (m, 8H), 4.61-4.86 (m, 3H), 5.48 (s, 0.5H), 5.49 (s, 0.5H), 6.36 (s, 0.5H), 6.37 (s, 0.5H), 6.65 (s, 0.5H), 6.69-6.71 (m, 1H), 6.75 (s, 0.5H), 6.95 (t, 1H), 7.07 (brd, 2H), 7.18-7.40 (m, 8H)	802.5
34		(600 MHz) 0.74-0.83 (m, 6H), 0.91-1.24 (m, 6H), 1.38-1.66 (m, 16H), 2.16 (s, 3H), 2.52-2.74 (m, 2H), 3.0 (dd, 1H), 3.11 (dd, 1H), 3.22 (brs, 2H), 3.55-3.90 (m, 2H), 3.96 (brd, 2H), 4.68 (ABq, 2H), 5.44 (s, 1H), 6.71 (s, 1H), 6.95 (t, 1H), 7.08 (brd, 2H), 7.26 (t, 2H), 7.28-7.32 (m, 1H), 7.34 (t, 2H), 7.38 (s, 1H), 7.42 (brd, 2H)	807.6
35		(600 MHz) 0.71 (brt, 6H), 0.93-1.18 (m, 4H), 1.18-1.58 (m, 4H), 2.04 (s, 3H), 3.0-3.2 (m, 4H), 3.49-3.76 (m, 2H), 3.94-4.04 (m, 2H), 5.32-5.34 (m, 1H), 6.45 (s, 1H), 6.86-6.94 (m, 3H), 7.16 (t, 2H), 7.27-7.38 (m, 4H), 7.47 (brd, 2H), 7.82 (brd, 2H), 8.05 (brd, 2H)	788.5

36		(600 MHz) 0.73-0.83 (m, 6H), 0.98-1.3 (m, 4H), 1.3-1.64 (m, 4H), 2.14 (s, 3H), 3.05-4.0 (m, 8H), 4.66 (ABq, 2H), 5.46 (s, 1H), 6.69 (s, 1H), 6.92 (t, 1H), 6.95 (t, 1H), 7.08 (brd, 2H), 7.2-7.3 (m, 5H), 7.35-7.39 (m, 3H), 8.44 (d, 2H)	774.5
37		0.73-0.84 (m, 6H), 0.98-1.3 (m, 4H), 1.3-1.65 (m, 4H), 2.14 (s, 3H), 3.04-4.1 (m, 8H), 4.66 (ABq, 2H), 5.47 (s, 1H), 6.70 (s, 1H), 6.97 (brt, 2H), 7.02 (d, 1H), 7.09 (brd, 2H), 7.2-7.32 (m, 5H), 7.35-7.43 (m, 3H), 7.72 (brt, 1H), 8.12 (brd, 1H)	773.5
38		0.74-0.85 (m, 6H), 0.86-1.3 (m, 4H), 1.3-1.65 (m, 4H), 2.15 (s, 3H), 3.21 (brs, 2H), 3.51-4.12 (m, 6H), 4.69 (ABq, 2H), 5.53 (s, 1H), 6.71 (s, 1H), 6.90 (d, 2H), 6.96 (t, 1H), 7.08 (d, 2H), 7.22-7.34 (m, 5H), 7.36-7.43 (m, 3H), 7.79 (d, 2H)	773.5
39		0.74-0.85 (m, 6H), 1.0-1.3 (m, 4H), 1.3-1.66 (m, 4H), 2.16 (s, 3H), 3.13-3.45 (m, 8H), 3.6-4.0 (m, 4H), 4.70 (ABq, 2H), 5.45 (s, 1H), 6.72 (s, 1H), 6.96 (t, 1H), 7.09 (brd, 2H), 7.22-7.45 (m, 8H)	722.5

Example 40

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[N-{(R)- α -[N'-(3-aminobenzyl)carbamoyl]benzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[N-{(R)- α -{N'-[3-(*t*-butoxycarbonylamino)benzyl]carbamoyl}benzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 25; 10 mg, 0.012 mmol) was dissolved in EtOAc (15 ml) saturated with HCl (gas). The reaction mixture was left for 1 hour. The solvent was evaporated under reduced pressure and the residue was freeze-dried to give the title compound in quantitative yield. NMR (600 MHz) 0.67-0.76 (m, 6H), 0.93-1.17 (m, 4H), 1.31-1.54 (m, 4H), 2.05 (s, 3H), 3.14 (brs, 2H), 3.44-3.86 (m, 2H), 4.25 (d, 1H), 4.40 (d, 1H), 4.64 (ABq, 2H), 5.40 (s, 1H), 6.62 (s, 1H), 6.88 (t, 1H), 7.01 (brd, 2H), 7.05-7.13 (m, 3H), 7.18 (t, 2H), 7.23-7.33 (m, 5H), 7.37 (d, 2H); *m/z* 715.5.

Example 41

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)- α -[N'-(piperidin-4-ylmethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)- α -[N'-(N''-t-butoxycarbonylpiperidin-4-ylmethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 34; 7.3 mg, 0.00904 mmol) was dissolved in ethyl acetate saturated with hydrogen chloride gas (15 ml). After 1.5 hours the reaction mixture was evaporated under reduced pressure. The product was lyophilised giving 4.6mg (68%) of the title compound. NMR (400 MHz): 0.74-0.87 (m, 6H), 0.9-1.7 (m, 10H), 1.73-1.9 (m, 3H), 2.15 (s, 3H), 2.83-2.98 (m, 2H), 3.04-3.40 (m, 6H), 3.6-3.9 (m, 2H), 4.71 (ABq, 2H), 5.42 (s, 1H), 6.72 (s, 1H), 6.97 (t, 1H), 7.09 (brd, 2H), 7.22-7.49 (m, 8H); 707.6.

Example 41

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(N-{(R)- α -[N'-(4-amidinobenzyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine acetate salt (Compound 1)

Example 42

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-8-(N-{(R)- α -[N'-(4-amidinobenzyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine acetate salt (Compound 2)

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[N-((R)- α -{N'-[4-(N²-benzyloxycarbonylamidino)benzyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 26; 18 mg, 0.020 mmol) was dissolved in ethanol (10 ml), palladium on activated carbon (5%, 10 mg) was added and a few drops of acetic acid. The mixture was treated under a hydrogen atmosphere for a couple of hours. The mixture was filtered through diatomaceous earth and the solvent was evaporated under reduced pressure. The reaction was not complete. The above had to be repeated two times. The mixture was purified by preparative HPLC using a MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give Compound 1, 1 mg (6%) and Compound 2, 1mg, 6%. Compound 1, m/z 742.5. Compound 2 NMR (400 MHz): 0.8-0.85 (m, 6H), 1.0-1.7 (m, 8H), 1.9 (s, 3H(acetate)), 3.23 (bs, 2H), 3.6-3.85 (m, 2H), 4.49 (ABq, 2H), 4.66 (s, 2H), 5.51 (s, 1H), 6.94

(d, 2H), 7.04 (d, 2H), 7.13 (dd, 1H), 7.23 (brt, 2H), 7.3-7.46 (m, 6H), 7.53 (d, 1H), 7.69 (d, 2H).

Example 43

5 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)- α -[N'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{N-[(R)- α -(carboxy)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 2 of
10 WO 02/50051; 81 mg, 0.124 mmol), (2*R*,3*R*,4*R*,5*S*)-6-aminohexane-1,2,3,4,5-pentol (26.9 mg, 0.15 mmol) and 2,6-dimethylpyridine (28.8 μ l, 0.25 mmol) was dissolved in DMF (3 ml). TBTU (48mg, 0.15 mmol) was added. The reaction mixture was stirred for 3-4 hours. The solvent was evaporated under reduced pressure. The product was purified by preparative HPLC using a MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent to give 59
15 mg (58%) of the title compound. NMR (600 MHz) 0.79 (t, 6H), 1.0-1.25 (m, 8H), 1.36-1.54 (m, 4H), 2.13 (s, 3H), 3.19 (dd, 1H), 3.23 (bs, 2H), 3.49 (dd, 2H), 3.55-3.85 (m, 8H), 4.68 (ABq, 2H), 5.38 (s, 1H), 6.68 (s, 1H), 6.74 (d, 2H), 6.96 (t, 1H), 7.10 (brd, 2H), 7.21-7.29 (m, 4H), 7.37 (s, 1H).

20 **Example 44**

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(N-{(R)- α -[N'-methyl-N'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)-1'-phenyl-1'-carboxymethyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Example 1 of WO 02/50051; 40
25 mg, 0.063 mmol), (2*R*,3*R*,4*R*,5*S*)-6-(methylamino)hexane-1,2,3,4,5-pentol (16 mg, 0.082 mmol) and N-Methylmorpholine (30 mg, 0.30 mmol) was dissolved in DMF (1 ml). TBTU (25 mg, 0.078 mmol) was added. The mixture was stirred for 1 hour. The solvent was evaporated under reduced pressure. The product was purified by preparative HPLC using a
30 MeCN/ammonium acetate buffer to give, after lyophilisation, 6 mg (12%) of the title compound. M/z 817.2.

Preparation of Starting Materials

The starting materials for the Examples above are either commercially available or are readily prepared by standard Methods from known materials. For Example, the following reactions are an illustration, but not a limitation, of some of the starting materials used in the
5 above reactions.

Method 1

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl)
carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

10 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-[N-((R)- α -carboxybenzyl)
carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 2; 50 mg, 0.078 mmol)
was dissolved in DMF (1.5 ml). Sodium methanethiolate (20 mg, 0.29 mmol) was added and
the mixture was stirred for 1.5 hours at 50°C. Acetic acid (40 mg) was added and the solvent
was evaporated under reduced pressure. The residue was purified by preparative HPLC using
15 MeCN/ammonium acetate buffer (45:55) as eluent to give the title compound 29 mg (61%).
NMR (400 MHz, DMSO- d_6): 0.7-0.8 (m, 6H), 0.9-1.6 (m, 8H), 2.2 (s, 3H), 3.1-3.7 (m, 4H),
4.6-4.8 (m, 3H), 6.7 (s, 1H), 6.8-7.4 (m, 11H), 8.3 (d, 1H).

Method 2

20 1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-[N-((R)- α -carboxybenzyl)
carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

The title compound was synthesised from 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-
bromo-8-[N-((R)- α -methoxycarbonylbenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-
benzothiazepine (Method 3) by the procedure of Example 9, except that the water layer was
25 extracted with EtOAc. The product was purified by preparative HPLC using an
MeCN/ammonium acetate buffer gradient (5/95 to 100/0) as eluent. NMR (400 MHz):
0.75-0.83 (m, 6H), 1.0-1.25 (m, 4H), 1.32-1.52 (m, 3H), 1.55-1.70 (m, 1H), 3.20 (ABq, 2H),
3.65-3.83 (m, 2H), 4.62 (ABq, 2H), 5.68 (d, 1H), 7.04-7.15 (m, 4H), 7.3-7.5 (m, 8H), 7.87
(brd, 1H); m/z 643.1.

Method 3**1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-[N-((R)- α -methoxycarbonylbenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine**

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (50 mg, 0.098 mmol) was dissolved in DCM (2 ml). Methyl (2R)-amino(phenyl)acetate hydrochloride (23.7 mg, 0.12 mmol) and DIPEA (0.068 ml, 0.39 mmol) was added and the reaction was stirred for 2 minutes. TBTU (38 mg, 0.12 mmol) was added and the mixture was stirred for 1.5 hours at room temperature. The mixture was directly put on an ISOLUTE-column (Silica, 2 g) and eluted stepwise with 10 ml DCM/EtOAc 100:1,9:1 then 8:2. 58 mg (90%) of the title compound was obtained. M/z 657.5

Method 4**1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine**

1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 5; 0.34 g) and sodium hydroxide (0.3 g) were dissolved in ethanol and the mixture was heated to reflux for 1 hour. Acetic acid (1 ml) was added and the solvent was removed at reduced pressure. The residue was partitioned between DCM/H₂O and the organic layer was separated and dried. Trituration of the residue with *n*-hexane gave the title compound 0.29 g (90%) as a solid. NMR (500 MHz, CDCl₃): 0.7-0.8 (m, 6H), 1.0-1.7 (m, 8H), 3.1-3.2 (m, 2H), 3.6 (br s, 2H), 4.6 (s, 2H), 6.9-7.1 (m, 4H), 7.2 (m, 2H), 7.5 (s, 1H).

Method 5**1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine**

A mixture of 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (WO 96/16051; 0.3 g), ethyl bromoacetate (0.14 g), sodium carbonate (0.3 g), tetrabutylammonium bromide (0.02 g) in MeCN (10 ml) were refluxed for 4 hours. The solvent was removed under reduced pressure. The residue was partitioned between DCM/H₂O and the organic layer was separated. The solvent was evaporated and the residue was purified by chromatography (DCM/EtOAc, 90:10) to give the title compound 0.34 g

(95%). NMR (500 MHz; CDCl₃): 0.7-0.9 (m, 6H), 1.0-1.8 (m, 11H), 3.2 (m, 2H), 3.6-3.8 (br s, 2H), 4.3 (q, 2H), 4.7 (s, 2H), 7.0-7.1 (m, 3 H), 7.15 (s, 1H), 7.3 (m, 2H), 7.4 (s, 1H).

Method 6

5 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- α -[*N'*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- α -[*N'*-(*t*-butoxycarbonylmethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 7; 120 mg, 0.17 mmol) was dissolved in DCM (2 ml). TFA (0.7 ml) was added and
10 the mixture was stirred at room temperature for 3 h. The reaction mixture was evaporated under reduced pressure. The residue was purified by preparative HPLC using MeCN/ammonium acetate buffer (50:50) as eluent to give the title compound 95 mg (85%). NMR (300 MHz, DMSO-*d*₆): 0.7-0.8 (m, 6H), 0.9-1.6 (m, 12H), 2.2 (s, 3H) 3.2-3.3 (m, 2H), 3.5-3.8 (m, 4H), 4.8 (ABq, 2H), 5.6 (d, 1H), 6.7 (s, 1H), 6.8-7.5 (m, 11H), 8.5-8.7 (m, 2H).

15

Method 7

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)- α -[*N'*-(*t*-butoxycarbonylmethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((*R*)- α -carboxybenzyl)
20 carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 8; 110 mg, 0.17 mmol), glycine tert-butyl ester (30 mg, 0.23 mmol) and DIPEA (120 mg, 0.93 mmol) were dissolved in DCM (2 ml). The mixture was stirred for 5 mins at room temperature. TBTU (72 mg, 0.22 mmol) was added and the mixture was stirred for 1 h at room temperature. The solvent was evaporated at reduced pressure and the residue was placed on a silica column and the product
25 was eluted with DCM/EtOAc (90:10) to give the title compound 122 mg (94%). NMR (300 MHz): 0.7-0.8 (m, 6H), 1.0-1.6 (m, 21H), 2.2 (s, 3H) 3.2 (s, 2H), 3.7-4.0 (m, 4H), 4.6 (ABq, 2H), 5.6 (d, 1H), 6.4 (t, 1H), 6.6 (s, 1H), 6.9-7.5 (m, 11H), 8.1 (d, 1H).

Method 81,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -carboxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -methoxycarbonylbenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 9; 300 mg, 0.46 mmol) was dissolved in methanol (5 ml). NaOH (100 mg in 0.2 ml water) was added to the solution and the mixture was stirred at room temperature for 1 hour. Acetic acid (0.3 ml) was added. The solvent was evaporated under reduced pressure and the residue was extracted with DCM/water. The DCM layer was separated, dried and evaporated under reduced pressure to give the title compound 270 mg (92%). NMR, 500 MHz): 0.7-0.8 (m, 6H), 1.0-1.6 (m, 12H), 2.1 (s, 3H) 3.2 (brs, 2H), 3.6-3.8 (m, 2H), 4.6 (s, 2H), 5.6 (d, 1H), 6.6 (s, 1H), 6.9-7.5 (m, 11H), 7.8 (d, 1H).

Method 91,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[N-((R)- α -methoxycarbonylbenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 10; 250 mg, 0.49 mmol), (R)-2-phenylglycine methyl ester hydrochloride (120 mg, 0.60 mmol) and DIPEA (300 mg, 2.3 mmol) were dissolved in DCM (10 ml) and the mixture was stirred for 5 min in room temperature. TBTU (210 mg, 0.65 mmol) was added and the mixture was stirred for 30 min at room temperature. The solvent was evaporated under reduced pressure and the residue was placed on a silica column and the product was eluted with DCM/EtOAc (90:10) to give the title compound 306 mg (95%). NMR (500 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 12H), 2.1 (s, 3H) 3.2 brs, 2H), 3.6-3.8 (m, 5H), 4.6 (ABq, 2H), 5.6 (d, 1H), 6.6 (s, 1H), 6.9-7.5 (m, 11H), 7.9 (d, 1H).

Method 101,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 11; 500 mg, 0.93 mmol) was dissolved in DMF (10 ml). Sodium methanethiolate (200 mg, 2.85 mmol) was added and the mixture was stirred for 2 hours at

50°C. Acetic acid (0.4 ml) was added and the solvent was evaporated under reduced pressure. The residue was extracted with EtOAc/water. The EtOAc layer was separated, dried and evaporated under reduced pressure to give the title compound 450 mg (96%). NMR (300 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 12H), 2.2 (s, 2H), 3.2 (brs, 2H), 3.7 (brs, 2H), 4.8 (s, 2H),
5 6.6 (s, 1H), 6.9-7.1 (m, 3H), 7.2-7.4 (m, 3H).

Method 11

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

10 1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 12; 2.2 g, 3.88 mmol) was dissolved in ethanol (15 ml). NaOH (0.8 g in 1.5 ml water) was added to the solution and the mixture was stirred for 30 min at room temperature. Acetic acid (2 ml) was added. The solvent was evaporated under reduced pressure and the residue was extracted with EtOAc/water. The EtOAc layer was
15 separated, dried and evaporated under reduced pressure to give the title compound 2.0 g (95%). NMR (500 MHz) 0.7-0.8 (m, 6H), 1.0-1.5 (m, 12H), 3.2 (brs, 2H), 3.7 (brs, 2H), 4.7 (s, 2H), 7.0-7.3 (m, 6H), 7.4 (s, 1H).

Method 12

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-bromo-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (synthesised by the procedure of WO9616051 for the corresponding 3-butyl-3-ethyl analogue; 2.0 g, 4.16 mmol), ethyl bromoacetate (0.84 g, 5.03 mmol), sodium
25 carbonate (2.0 g, 18.9 mmol) and tetrabutylammonium bromide (80 mg, 0.25 mmol) were added to MeCN (20 ml). The mixture was refluxed for 2 hours and then evaporated under reduced pressure. The residue was extracted with DCM/water. The DCM layer was separated and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel. The product was eluted with DCM / EtOAc (90:10) to give the title compound
30 2.2 g (93%). NMR (400 MHz) 0.7-0.8 (m, 6H), 1.0-1.6 (m, 15H), 3.2 (brs, 2H), 3.7 (brs, 2H), 4.3 (q, 2H), 4.7 (s, 2H), 7.0-7.3 (m, 6H), 7.4 (s, 1H).

Method 13**5,6-Dimethoxy-2,3-dihydrobenzofuran-2-ylmethylamine**

5,6-Dimethoxy-2,3-dihydrobenzofuran-2-carbonitrile (Method 16; 2.63 g, 12.94 mmol) was dissolved in ethanol (700 ml) and hydrochloric acid (conc, 2.3 ml) and Pd on charcoal (10%, 1 g) were added. The mixture was hydrogenated under 3.5 atmosphere of hydrogen at 72°C for 3 days. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in water and washed once with diethyl ether. The pH of the aqueous phase was adjusted to 10-11 with NaOH(aq) and the resulting solution was extracted several times with diethyl ether, then with DCM. The organic layers were dried, filtered and evaporated under reduced pressure. The diethyl ether extraction gave 0.6 g (22%) of pure product and the DCM extraction gave 2.0 g (74%) of pure product. NMR (400 MHz) 2.80-2.87 (m, 3H), 3.21 (dd, 1H), 3.74 (s, 3H), 3.76 (s, 3H), 4.72-4.82 (m, 1H), 6.47 (s, 1H), 6.82 (s, 1H).

Method 14**N-(2-Aminoethyl)-N'-pyrimidin-2-ylurea**

Phenyl pyrimidin-2-ylcarbamate (121.3 g, 0.57 mol) and ethane-1,2-diamine (380 ml, 5.7 mol) were mixed and cooled with an ice-bath. Sodium (0.5 g, 0.0217 mol) was added in small pieces. The reaction was exothermic and the temperature went up to 38°C and then the temperature was kept at approximately 8°C for 5 days. The remaining ethane-1,2-diamine was evaporated under reduced pressure and co-evaporated with toluene three times. The residue was dissolved in ethanol (99%, 1l) and filtered. Hydrochloric acid (conc, 78 ml) was added. The mixture was kept at 8°C overnight. The crystals formed were collected and washed with ethanol (99%) to yield the product as a HCl-salt in 97% (120 g) yield. NMR (400 MHz) 3.15 (t, 2H), 3.27 (brs, NH), 3.63 (t, 2H), 7.05 (t, 1H), 8.57 (d, 2H).

Method 15**N-(2-Aminoethyl)-N'-pyridin-2-ylurea**

Phenyl pyridin-2-ylcarbamate (163.5 g, 0.929 mol) and ethane-1,2-diamine (620 ml, 9.29 mol) was mixed and cooled with an ice-bath. Sodium (0.5 g, 0.0217 mol) was added in small pieces. The reaction was exothermic and the temperature went up to 42°C and then the temperature was kept at 8°C for 5 days. The remaining ethane-1,2-diamine was evaporated under reduced pressure and co-evaporated with toluene three times. The residue was dissolved

in MeCN and the crystals formed were filtered off. Hydrochloric acid (conc, 110 ml) was added to the solution. The crystals formed were collected and washed with MeCN:MeOH 1:1 to yield the product as a HCl-salt in 72% (145.1 g) yield. NMR (400 MHz) 3.16 (t, 2H), 3.28 (brs, NH), 3.60 (t, 2H), 7.40-7.47 (m, 2H), 8.27-8.36 (m, 2H).

5

Method 16**5,6-Dimethoxy-2,3-dihydrobenzofuran-2-carbonitrile**

2-Hydroxy-4,5-dimethoxybenzaldehyde (25.5 g, 0.14 mol), chloroacetonitrile (12.4 g, 0.168 mol) and potassium carbonate (116 g, 0.84 mol) was dissolved in DMF (150 ml). The mixture was stirred for 10 minutes at 165°C. The solvent was concentrated under reduced pressure. The residue was separated in two parts, water was added and the first part was extracted with diethyl ether and the second part extracted with DCM. The second part was evaporated under reduced pressure and dissolved in ether and washed once with water. The organic layers was combined and evaporated under reduced pressure. The crystalline residue was washed with warm methanol (700 ml) and filtered. The residue was dissolved in 225 ml DCM and diethyl ether (450 ml) was added. The crystals formed was collected giving 14.6 g (51%yield) of product. Mp. 162°C.

Method 17**1,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-carboxymethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine**

To 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 18; 478 mg, 0.95 mmol) was added THF (15 ml), water (3 ml) and LiOH (34 mg, 1.4 mmol). The reaction was then stirred for 1 hour. Then acetic acid (0.2 ml) was added along with water (10 ml) and DCM (10 ml) The aqueous layer was then extracted three times with DCM. The combined organic phases were then dried and concentrated to give the title compound 450 mg (99%). NMR (400 MHz) 0.7-0.9 (m, 6H), 1.0-1.7 (m, 8H), 2.2 (s, 3H), 3.2 (q, 2H), 3.7 (m, 2H), 4.8 (s, 2H), 6.65 (s, 1H), 6.95 (t, 1H), 7.05 (d, 2H), 7.25 (t, 2H), 7.35 (s, 1H), 8.4 (brs, 1H).

30

Method 181,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-ethoxycarbonylmethoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

To 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (Method 19; 500 mg, 1.2 mmol) was added MeCN (30 ml),
5 tetrabutylammonium bromide (30 mg, 0.08 mmol), anhydrous sodium carbonate (500 mg, 4.7 mmol), ethyl bromoacetate (0.14 ml, 1.26 mmol) and caesium carbonate (20 mg, 0.06 mmol). This reaction mixture was then stirred over night at 80°C. Then the solvent was removed under reduced pressure, water and DCM were added and the aqueous phase was extracted
10 three times with DCM. The combined organic phases were then dried, concentrated and purified by flash chromatography [DCM : EtOAc, 1:0, 9:1] to give the title compound 600 mg (99%). NMR (300 MHz) 0.8-1.0 (m, 6H), 1.0-1.8 (m, 11H), 2.2 (s, 3H), 3.2 (q, 2H) 3.75 (brq, 2H), 4.3 (q, 2H), 4.75 (s, 1H), 6.7 (s, 1H), 6.95 (t, 1H), 7.05 (d, 2H), 7.25 (t, 2H), 7.3 (s, 1H).

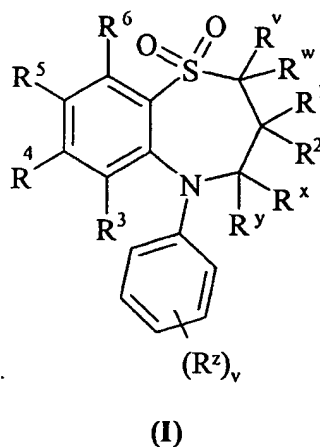
Method 191,1-Dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-hydroxy-2,3,4,5-tetrahydro-1,5-benzothiazepine

To 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-bromo-8-methoxy-2,3,4,5-tetrahydro-1,5-benzothiazepine (WO9616051; 600 mg, 1.29 mmol) were added DMF (5 ml) and sodium
20 methanethiolate (450 mg, 6.42 mmol). The reaction was then heated to 60°C for 1 hour. The oil bath was then heated to 120°C for 4 hours. To quench the reaction, the temperature was lowered to room temperature and excess acetic acid was added quickly. The reaction was kept under a flow of nitrogen through sodium hypochlorite for 2 hours. Water and EtOAc were added and the aqueous phase was extracted three times with EtOAc. The combined organic
25 phases were washed with water, dried and concentrated under reduced pressure. The residue was then purified by flash chromatography [DCM : EtOAc, 9:1] to give the title compound 0.5 g (92%). NMR (400 MHz) 0.65-0.8 (m, 6H), 0.95-1.6 (m, 8h), 3.1 (q, 2H), 3.6 (brq, 2H), 6.75 (s, 1H), 6.8 (t, 1H), 6.9 (d, 2H), 7.15 (t, 2H), 7.55 (s, 1H).

Claims

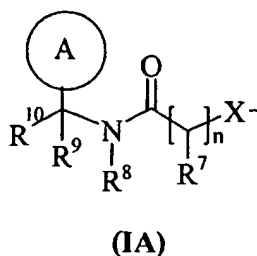
What we claim is:

- 5 1. A compound of formula (I):



wherein:

- R^v and R^w are independently selected from hydrogen or C_{1-6} alkyl;
- 10 One of R^1 and R^2 are selected from hydrogen or C_{1-6} alkyl and the other is selected from C_{1-6} alkyl;
- R^x and R^y are independently selected from hydrogen or C_{1-6} alkyl, or one of R^x and R^y is hydrogen or C_{1-6} alkyl and the other is hydroxy or C_{1-6} alkoxy;
- R^z is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto,
- 15 sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkylS(O) $_a$ wherein a is 0 to 2, C_{1-6} alkoxycarbonyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl) $_2$ sulphamoyl;
- v is 0-5;
- 20 one of R^4 and R^5 is a group of formula (IA):



R^3 and R^6 and the other of R^4 and R^5 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl)₂amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkylS(O)_a wherein a is 0 to 2, C_{1-6} alkoxycarbonyl, N -(C_{1-6} alkyl)sulphamoyl and N,N -(C_{1-6} alkyl)₂sulphamoyl; wherein R^3 and R^6 and the other of R^4 and R^5 may be optionally substituted on carbon by one or more R^{17} ;

X is -O-, -N(R^a)-, -S(O)_b- or -CH(R^a)-; wherein R^a is hydrogen or C_{1-6} alkyl and b is 0-2;

10 **Ring A** is aryl or heteroaryl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R^{18} ;

R^7 is hydrogen, C_{1-6} alkyl, carbocyclyl or heterocyclyl; wherein R^7 is optionally substituted on carbon by one or more substituents selected from R^{19} ; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{20} ;

R^8 is hydrogen or C_{1-6} alkyl;

R^9 is hydrogen or C_{1-6} alkyl;

R^{10} is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy, C_{1-10} alkanoyl, C_{1-10} alkanoyloxy, N -(C_{1-10} alkyl)amino, N,N -(C_{1-10} alkyl)₂amino, N,N,N -(C_{1-10} alkyl)₃ammonio, C_{1-10} alkanoylamino, N -(C_{1-10} alkyl)carbamoyl, N,N -(C_{1-10} alkyl)₂carbamoyl, C_{1-10} alkylS(O)_a wherein a is 0 to 2, N -(C_{1-10} alkyl)sulphamoyl, N,N -(C_{1-10} alkyl)₂sulphamoyl, N -(C_{1-10} alkyl)sulphamoylamino, N,N -(C_{1-10} alkyl)₂sulphamoylamino, C_{1-10} alkoxycarbonylamino, carbocyclyl,

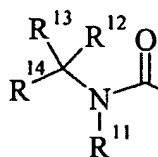
25 carbocyclyl C_{1-10} alkyl, heterocyclyl, heterocyclyl C_{1-10} alkyl,

carbocyclyl-(C_{1-10} alkylene)_p- R^{21} -(C_{1-10} alkylene)_q- or

heterocyclyl-(C_{1-10} alkylene)_r- R^{22} -(C_{1-10} alkylene)_s-; wherein R^{10} is optionally substituted on carbon by one or more substituents selected from R^{23} ; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from

30 R^{24} ; or R^{10} is a group of formula (IB):

- 76 -



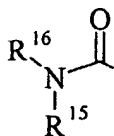
(IB)

wherein:

R^{11} is hydrogen or C_{1-6} alkyl;

- 5 R^{12} and R^{13} are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy, C_{1-10} alkanoyl, C_{1-10} alkanoyloxy, N -(C_{1-10} alkyl)amino, N,N -(C_{1-10} alkyl)₂amino, C_{1-10} alkanoylamino, N -(C_{1-10} alkyl)carbamoyl, N,N -(C_{1-10} alkyl)₂carbamoyl, C_{1-10} alkylS(O)_a wherein a is 0 to 2, N -(C_{1-10} alkyl)sulphamoyl, N,N -(C_{1-10} alkyl)₂sulphamoyl, 10 N -(C_{1-10} alkyl)sulphamoylamino, N,N -(C_{1-10} alkyl)₂sulphamoylamino, carbocyclyl or heterocyclyl; wherein R^{12} and R^{13} may be independently optionally substituted on carbon by one or more substituents selected from R^{25} ; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{26} ;

- R^{14} is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, 15 mercapto, sulphamoyl, hydroxyaminocarbonyl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy, C_{1-10} alkanoyl, C_{1-10} alkanoyloxy, N -(C_{1-10} alkyl)amino, N,N -(C_{1-10} alkyl)₂amino, N,N,N -(C_{1-10} alkyl)₃ammonio, C_{1-10} alkanoylamino, N -(C_{1-10} alkyl)carbamoyl, N,N -(C_{1-10} alkyl)₂carbamoyl, C_{1-10} alkylS(O)_a wherein a is 0 to 2, N -(C_{1-10} alkyl)sulphamoyl, N,N -(C_{1-10} alkyl)₂sulphamoyl, N -(C_{1-10} alkyl)sulphamoylamino, 20 N,N -(C_{1-10} alkyl)₂sulphamoylamino, C_{1-10} alkoxycarbonylamino, carbocyclyl, carbocyclyl C_{1-10} alkyl, heterocyclyl, heterocyclyl C_{1-10} alkyl, carbocyclyl-(C_{1-10} alkylene)_p- R^{27} -(C_{1-10} alkylene)_q- or heterocyclyl-(C_{1-10} alkylene)_r- R^{28} -(C_{1-10} alkylene)_s-; wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{29} ; and wherein if said heterocyclyl 25 contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{30} ; or R^{14} is a group of formula (IC):



(IC)

R^{15} is hydrogen or C_{1-6} alkyl;

R^{16} is hydrogen or C_{1-6} alkyl; wherein R^{16} may be optionally substituted on carbon by one or more groups selected from R^{31} ;

n is 1-3; wherein the values of R^7 may be the same or different;

5 $R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29}$ or R^{31} are independently selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphonamoyl, hydroxyaminocarbonyl, amidino, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} alkoxy, C_{1-10} alkanoyl, C_{1-10} alkanoyloxy, $(C_{1-10}alkyl)_3silyl$, $N-(C_{1-10}alkyl)amino$, $N,N-(C_{1-10}alkyl)_2amino$, $N,N,N-(C_{1-10}alkyl)_3ammonio$, $C_{1-10}alkanoylamino$, $N-(C_{1-10}alkyl)carbamoyl$, $N,N-(C_{1-10}alkyl)_2carbamoyl$, $C_{1-10}alkylS(O)_a$
 10 wherein a is 0 to 2, $N-(C_{1-10}alkyl)sulphonamoyl$, $N,N-(C_{1-10}alkyl)_2sulphonamoyl$, $N-(C_{1-10}alkyl)sulphonamoylamino$, $N,N-(C_{1-10}alkyl)_2sulphonamoylamino$, $C_{1-10}alkoxycarbonylamino$, carbocyclyl, carbocyclyl $C_{1-10}alkyl$, heterocyclyl, heterocyclyl $C_{1-10}alkyl$, carbocyclyl- $(C_{1-10}alkylene)_p-R^{32}-(C_{1-10}alkylene)_q-$ or heterocyclyl- $(C_{1-10}alkylene)_r-R^{33}-(C_{1-10}alkylene)_s-$; wherein $R^{17}, R^{18}, R^{19}, R^{23}, R^{25}, R^{29}$ or R^{31}
 15 may be independently optionally substituted on carbon by one or more R^{34} ; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{35} ;

$R^{21}, R^{22}, R^{27}, R^{28}, R^{32}$ or R^{33} are independently selected from -O-, $-NR^{36}-$, $-S(O)_x-$, $-NR^{36}C(O)NR^{36}-$, $-NR^{36}C(S)NR^{36}-$, $-OC(O)N=C-$, $-NR^{36}C(O)-$ or $-C(O)NR^{36}-$; wherein R^{36} is
 20 selected from hydrogen or C_{1-6} alkyl, and x is 0-2;

p, q, r and s are independently selected from 0-2;

R^{34} is selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carbamoyl, mercapto, sulphonamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, formyl, acetyl, formamido, acetylamino, acetoxymethyl, methylamino,
 25 dimethylamino, N -methylcarbamoyl, N,N -dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, N -methylsulphonamoyl, N,N -dimethylsulphonamoyl, N -methylsulphonamoylamino and N,N -dimethylsulphonamoylamino;

$R^{20}, R^{24}, R^{26}, R^{30}$ or R^{35} are independently selected from C_{1-6} alkyl, C_{1-6} alkanoyl, $C_{1-6}alkylsulphonyl$, $C_{1-6}alkoxycarbonyl$, carbamoyl, $N-(C_{1-6}alkyl)carbamoyl$,
 30 $N,N-(C_{1-6}alkyl)carbamoyl$, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

2. A compound of formula **(I)** as claimed in claim 1 wherein R^v and R^w are both hydrogen, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
- 5 3. A compound of formula **(I)** as claimed in either of claims 1 or 2 wherein one of R¹ and R² is ethyl and the other is butyl, or R¹ and R² are both butyl, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
- 10 4. A compound of formula **(I)** as claimed in any one of claims 1-3 wherein R^x and R^y are both hydrogen, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
5. A compound of formula **(I)** as claimed in any one of claims 1-4 wherein v is 0, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
- 15 6. A compound of formula **(I)** as claimed in any one of claims 1-5 wherein R³ and R⁶ are both hydrogen, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
- 20 7. A compound of formula **(I)** as claimed in any one of claims 1-6 wherein R⁴ is hydrogen or methylthio, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
8. A compound of formula **(I)** as claimed in any one of claims 1-7 wherein R⁵ is a group of formula **(IA)** as depicted above, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
- 25 9. A compound of formula **(I)** as claimed in any one of claims 1-8 wherein R⁵ is a group of formula **(IA)** as depicted above wherein:
- 30 X is -O-;
R⁷ is hydrogen;
R⁸ is hydrogen;

R⁹ is hydrogen;

Ring A is aryl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R¹⁸;

R¹⁰ is carbamoyl or *N*-(C₁₋₁₀alkyl)carbamoyl or a group of formula (IB) (as depicted above) wherein R¹⁰ is optionally substituted on carbon by one or more substituents selected from R²³ and wherein:

R¹¹ is hydrogen or C₁₋₆alkyl;

R¹² and R¹³ are independently selected from hydrogen, carbamoyl or C₁₋₆alkyl; wherein R¹² and R¹³ may be independently optionally substituted on carbon by one or more substituents selected from R²⁵;

R¹⁴ is selected from carbamoyl, hydroxyaminocarbonyl, C₁₋₆alkyl, carbocyclyl, heterocyclyl or carbocyclyl-(C₁₋₆alkylene)_p-R²⁷-(C₁₋₆alkylene)_q-; wherein R¹⁴ may be optionally substituted on carbon by one or more substituents selected from R²⁹; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R³⁰; or R¹⁴ is a group of formula (IC) (as depicted above) wherein:

R¹⁵ is hydrogen;

R¹⁶ is C₁₋₆alkyl; wherein R¹⁶ may be optionally substituted on carbon by one or more groups selected from R³¹;

n is 1;

R¹⁸ is hydroxy;

R²³ is hydroxy;

R²⁵, R²⁹ or R³¹ are independently selected from halo, hydroxy, amino, sulphamoyl, amidino, C₁₋₆alkoxy, *N,N,N*-(C₁₋₆alkyl)₃ammonio, *N,N*-(C₁₋₆alkyl)₂sulphamoylamino, C₁₋₆alkoxycarbonylamino, carbocyclyl, heterocyclyl, carbocyclyl-(C₁₋₆alkylene)_p-R³²-(C₁₋₆alkylene)_q- or heterocyclyl-(C₁₋₆alkylene)_r-R³³-(C₁₋₆alkylene)_s-; wherein R²⁵, R²⁹ or R³¹ may be independently optionally substituted on carbon by one or more R³⁴; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R³⁵;

R²⁷, R³² or R³³ are independently selected from -O-, -NR³⁶C(O)NR³⁶-, -OC(O)N=C- or -NR³⁶C(O)-; wherein R²³ is hydrogen;

p, q, r and s are independently selected from 0 or 1;

R³⁴ is selected from hydroxy, amino, carbamoyl, sulphamoyl or methoxy;

R^{30} or R^{35} are independently selected from C_{1-6} alkyl or C_{1-6} alkoxycarbonyl.
or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

10. A compound of formula **(I)** (as depicted above) wherein:
- 5 R^v and R^w are both hydrogen;
One of R^1 and R^2 is ethyl and the other is butyl or R^1 and R^2 are both butyl;
 R^x and R^y are both hydrogen;
 v is 0;
 R^3 and R^6 are hydrogen;
- 10 R^4 is hydrogen or methylthio;
 R^5 is a group of formula **(IA)** as depicted above wherein:
 X is -O-;
 R^7 is hydrogen;
 R^8 is hydrogen;
- 15 R^9 is hydrogen;
Ring A is aryl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from R^{18} ;
 R^{10} is carbamoyl or N -(C_{1-10} alkyl)carbamoyl or a group of formula **(IB)** (as depicted above) wherein R^{10} is optionally substituted on carbon by one or more substituents selected
- 20 from R^{23} and wherein:
 R^{11} is hydrogen or C_{1-6} alkyl;
 R^{12} and R^{13} are independently selected from hydrogen, carbamoyl or C_{1-6} alkyl;
wherein R^{12} and R^{13} may be independently optionally substituted on carbon by one or more substituents selected from R^{25} ;
- 25 R^{14} is selected from carbamoyl, hydroxyaminocarbonyl, C_{1-6} alkyl, carbocyclyl, heterocyclyl or carbocyclyl-(C_{1-6} alkylene) $_p$ - R^{27} -(C_{1-6} alkylene) $_q$ -; wherein R^{14} may be optionally substituted on carbon by one or more substituents selected from R^{29} ; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R^{30} ; or R^{14} is a group of formula **(IC)** (as depicted above) wherein:
- 30 R^{15} is hydrogen;
 R^{16} is C_{1-6} alkyl; wherein R^{16} may be optionally substituted on carbon by one or more groups selected from R^{31} ;

n is 1;

R¹⁸ is hydroxy;

R²³ is hydroxy;

R²⁵, R²⁹ or R³¹ are independently selected from halo, hydroxy, amino, sulphamoyl, amidino, C₁₋₆alkoxy, *N,N,N*-(C₁₋₆alkyl)₃ammonio, *N,N*-(C₁₋₆alkyl)₂sulphamoylamino, C₁₋₆alkoxycarbonylamino, carbocyclyl, heterocyclyl, carbocyclyl-(C₁₋₆alkylene)_p-R³²-(C₁₋₆alkylene)_q- or heterocyclyl-(C₁₋₆alkylene)_r-R³³-(C₁₋₆alkylene)_s-; wherein R²⁵, R²⁹ or R³¹ may be independently optionally substituted on carbon by one or more R³⁴; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from R³⁵;

R²⁷, R³² or R³³ are independently selected from -O-, -NR³⁶C(O)NR³⁶-, -OC(O)N=C- or -NR³⁶C(O)-; wherein R²³ is hydrogen;

p, q, r and s are independently selected from 0 or 1;

R³⁴ is selected from hydroxy, amino, carbamoyl, sulphamoyl or methoxy;

R³⁰ or R³⁵ are independently selected from C₁₋₆alkyl or C₁₋₆alkoxycarbonyl.
or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

11. A compound of formula (I) selected from:

- 20 1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 25 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(S)-1-carbamoyl-2-hydroxyethyl]carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(hydroxycarbamoylmethyl)carbamoyl]benzyl} carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
- 30 1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-{*N'*-[2-(*N'*-pyrimidin-2-ylureido)ethyl]carbamoyl} benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((*R*)- α -{*N'*-[2-(*N'*-pyridin-2-ylureido)ethyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N'*-(1-*t*-butoxycarbonylpiperidin-4-ylmethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-

5 tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N'*-(2,3-dihydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)- α -{*N'*-[2-(3,4-dihydroxyphenyl)-2-methoxyethyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-

10 benzothiazepine

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N'*-(2-aminoethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N'*-(piperidin-4-ylmethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; or

15

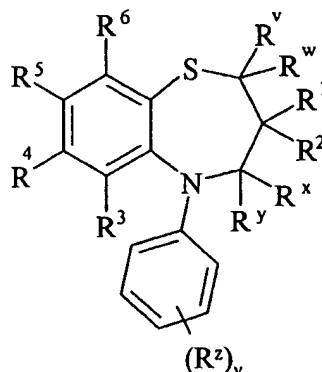
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)- α -[*N'*-(2-*N,N*-dimethylaminosulphamoyl)ethyl]carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

20

12. A process for preparing a compound of formula (I), as claimed in any one of claims 1-11, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof which process comprises of:

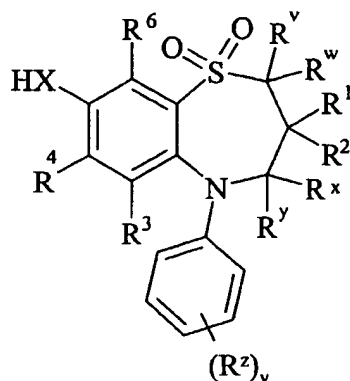
Process 1): oxidising a benzothiazepine of formula (II):



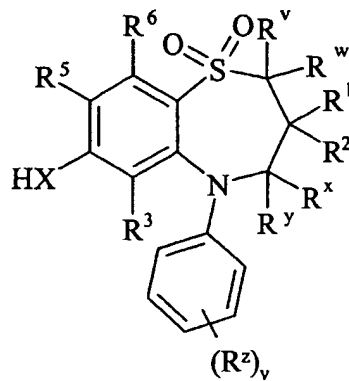
(II);

25

Process 2): for compounds of formula (I) wherein X is -O-, -NR^a or -S-; reacting a compound of formula (IIIa) or (IIIb):

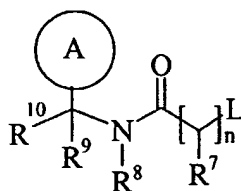


(IIIa)



(IIIb)

5 with a compound of formula (IV):

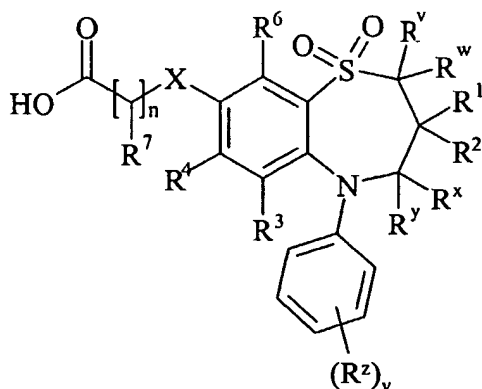


(IV)

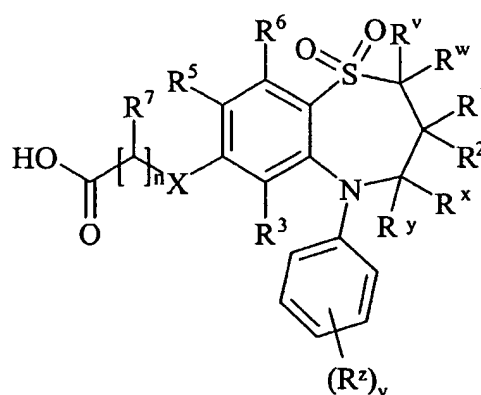
wherein L is a displaceable group;

Process 3): reacting an acid of formula (Va) or (Vb):

10



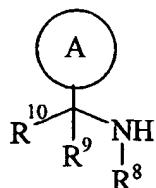
(Va)



(Vb)

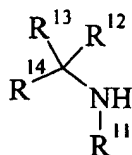
or an activated derivative thereof; with an amine of formula (VI):

- 84 -



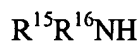
(VI);

Process 4): for compounds of formula (I) wherein R^{10} is a group of formula (IB); reacting a compound of formula (I) wherein R^{10} is carboxy with an amine of formula (VII):



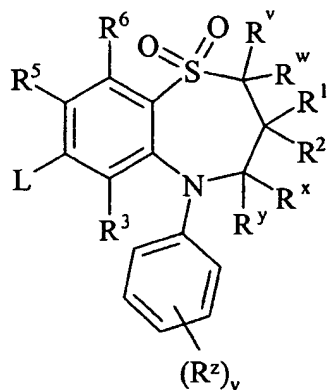
(VII)

Process 5): for compounds of formula (I) wherein R^{10} is a group of formula (IB) and R^{14} is a group of formula (IC) reacting a compound of formula (I) wherein R^{14} is carboxy with an amine of formula (VIII):

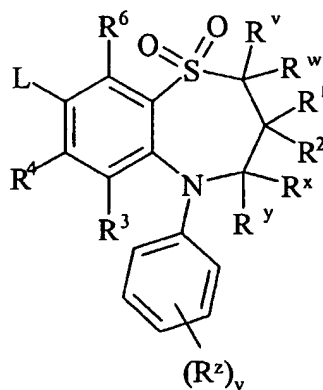


(VIII)

Process 6) for compounds of formula (I) wherein one of R^4 and R^5 are independently selected from C_{1-6} alkylthio optionally substituted on carbon by one or more R^{17} ; reacting a compound of formula (IXa) or (IXb):



(IXa)



(IXb)

wherein L is a displaceable group; with a thiol of formula (X):



(X)

wherein R^y is C_{1-6} alkylthio optionally substituted on carbon by one or more R^{16} ;

and thereafter if necessary or desirable:

- i) converting a compound of the formula (I) into another compound of the formula (I);
- ii) removing any protecting groups;
- iii) forming a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug.

5

13. A compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 11 for use as a medicament.

10

14. A compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 11 for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

15

15. The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 11 in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

20

16. The use of a compound of the formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 11, in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

25

17. A method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 11.

30

18. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 11, in association with a pharmaceutically-acceptable diluent or carrier.

19. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 11, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.
20. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 11, and a bile acid binder, in association with a pharmaceutically acceptable diluent or carrier.
21. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 11, and an HMG Co-A reductase inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a bile acid binder in association with a pharmaceutically acceptable diluent or carrier.
22. A composition according to claim 19 or claim 21 wherein the HMG Co-A reductase inhibitor is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.
23. A composition according to claim 19 or claim 21 wherein the HMG Co-A reductase inhibitor is rosuvastatin, or a pharmaceutically acceptable salt thereof.
24. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, as claimed in any one of claims 1 to 11 and a PPAR alpha and/or gamma agonist, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

25. A composition according to claim 24 wherein the PPAR alpha and/or gamma agonist is (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxyphenyl}ethoxy)phenyl]propanoic acid or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

PCT/GB 02/03983

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D281/10 C07D417/12 A61K31/554 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 01 66533 A (ASTRAZENECA UK LTD ; DAHLSTROM MICHAEL (SE); ASTRAZENECA AB (SE); B) 13 September 2001 (2001-09-13) claims; examples ---	1-25
P,Y	WO 02 50051 A (ASTRAZENECA UK LTD ; ASTRAZENECA AB (SE); BLOMBERG DAVID (SE); STAR) 27 June 2002 (2002-06-27) claims; examples ---	1-25
A	EP 0 864 582 A (HOECHST AG) 16 September 1998 (1998-09-16) cited in the application claims; examples ---	1-25
	--- -/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

16 October 2002

Date of mailing of the international search report

25/10/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo.nl,
Fax: (+31-70) 340-3016

Authorized officer

Menegaki, F

INTERNATIONAL SEARCH REPORT

PCT/GB 02/03983

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 96 05188 A (WELLCOME FOUND ;BRIEADDY LAWRENCE EDWARD (US)) 22 February 1996 (1996-02-22) cited in the application claims; examples -----</p>	1-25

INTERNATIONAL SEARCH REPORT

PCT/GB 02/03983

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 16,17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB 02/03983

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0166533	A	13-09-2001	AU 3755601 A WO 0166533 A1	17-09-2001 13-09-2001
WO 0250051	A	27-06-2002	AU 2222802 A WO 0250051 A1	01-07-2002 27-06-2002
EP 0864582	A	16-09-1998	EP 0864582 A2 AU 731575 B2 BR 9801126 A CA 2231971 A1 CN 1194979 A , B CZ 9800759 A3 HU 9800541 A2 IL 123648 A JP 3282998 B2 JP 10279568 A NZ 329932 A PL 325363 A1 RU 2179977 C2 TR 9800444 A2 US 6020330 A US 6114322 A ZA 9802140 A	16-09-1998 05-04-2001 21-03-2000 14-09-1998 07-10-1998 16-09-1998 28-06-1999 21-11-2000 20-05-2002 20-10-1998 28-01-1999 28-09-1998 27-02-2002 21-10-1998 01-02-2000 05-09-2000 14-09-1998
WO 9605188	A	22-02-1996	AP 720 A AU 696073 B2 AU 4426096 A BG 62048 B1 BG 101209 A BR 9508586 A CA 2197099 A1 CN 1161035 A , B CZ 9700373 A3 EE 9700028 A EP 1203769 A1 EP 0775126 A1 FI 970531 A WO 9605188 A1 HU 77129 A2 IL 114877 A JP 2935756 B2 JP 10504035 T NO 970585 A NZ 290911 A PL 318496 A1 RU 2156245 C2 SK 17797 A3	08-01-1999 03-09-1998 07-03-1996 29-01-1999 29-08-1997 14-07-1998 22-02-1996 01-10-1997 13-08-1997 15-08-1997 08-05-2002 28-05-1997 07-02-1997 22-02-1996 02-03-1998 14-07-1999 16-08-1999 14-04-1998 07-04-1997 28-07-1998 23-06-1997 20-09-2000 10-09-1997